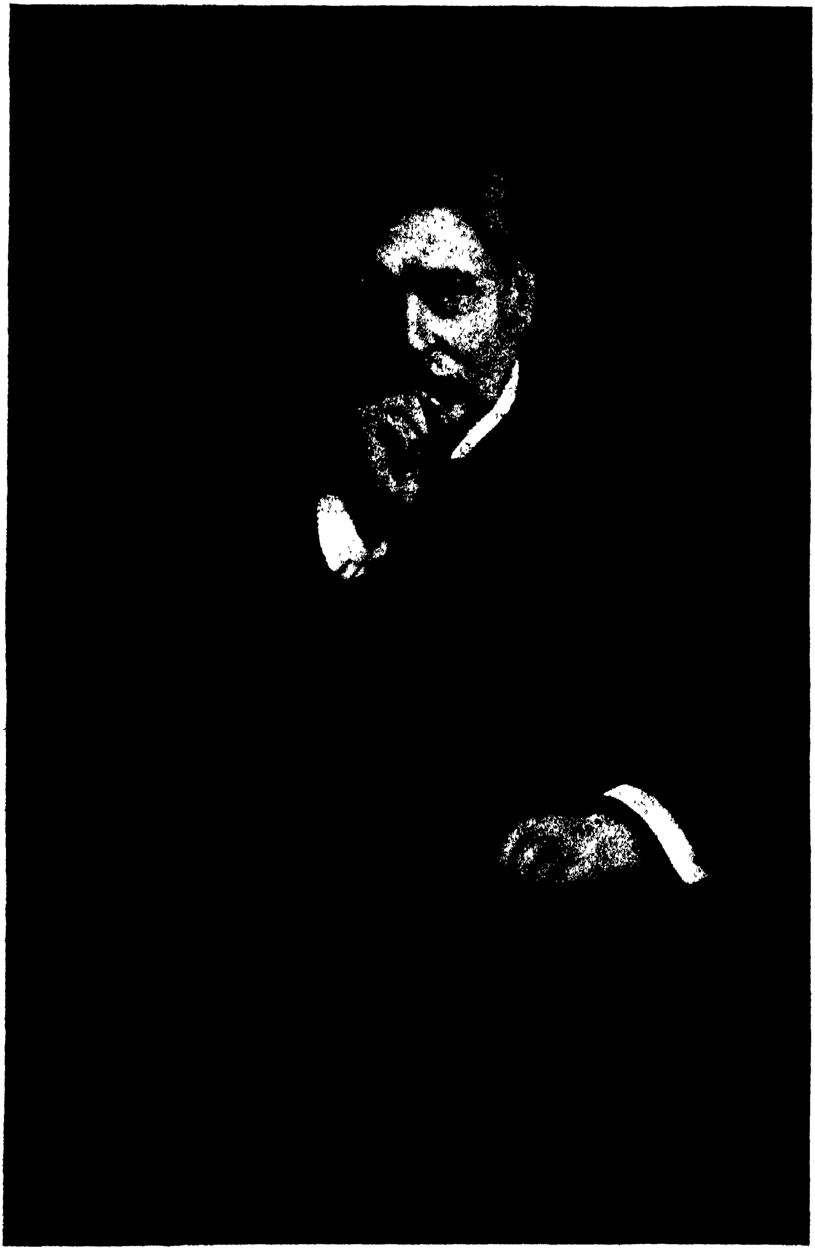
06170



SIR PATRICK MANSON, G.C.M.G., F.R.S.

PLATE I

MANSON'S TROPICAL DISEASES

A MANUAL OF THE DISEASES OF WARM CLIMATES

EDITED BY

PHILIP H. MANSON-BAHR

C.M.G., D.S.O., M.A., M.D., D.T.M. AND H. CANTAB.,
F.R.C.P. LOND.

Senior Physician to the Hospital for Tropical Diseases, London, the Albert Dock Hospital and the Tilbury Hospital; Consulting Physician to the Colonial Office and Crown Agents for the Colonies; Consultant in Tropical Diseases to the Admiralty and to the Royal Air Force; Director, Division of Clinical Medicine, London School of Hygiene and Tropical Medicine; Lecturer on Tropical Medicine to the London Hospital; Corresponding Member of the Société de Pathologie Exotique; Member of the Washington Academy of Medicine; late Examiner in Tropical Medicine to the Conjoint Board of the Royal College of Physicians and Royal College of Surgeons, England, and to Cambridge and Hongkong Universities. Author (with A. Alcock) of "The Life and Work of Sir Patrick Manson," 1927; "The Dysenteric Disorders," 1939 and "Synopsis of Tropical Medicine", 1943.

Twelfth Edition

WITH 17 COLOUR PLATES, 9 HALF-TONE PLATES,
406 FIGURES IN THE TEXT, 6 MAPS, AND 28 CHARTS

CASSELL AND COMPANY, LTD
London, Toronto, Melbourne and Sydney
1945

First Published	*May*	1898
Reprinted ..	*July*	1898
,, ..	*September*	1898
,, ..	*January*	1899
Second Edition		1900
Reprinted ..	*January*	1901
Third Edition	*April*	1903
Reprinted ..	*August*	1903
,, ..	*October*	1904
Fourth Edition	*August*	1907
Reprinted ..	*March*	1908
,, ..	*August*	1909
,, ..	*March*	1911
,, ..	*March*	1912
Fifth Edition ..	*May*	1914
Sixth Edition ..	*October*	1917
Reprinted ..	*January*	1918
,, ..	*February*	1919
Seventh Edition	*February*	1921
Reprinted ..	*July*	1923
Eighth Edition	*March*	1925
Reprinted ..	*June*	1927
Ninth Edition	*February*	1929
Reprinted ..	*March*	1931
Tenth Edition	*November*	1935
Eleventh Edition	*April*	1940
Reprinted ..	*January*	1941
,, ..	*September*	1942
Twelfth Edition	*August*	1945

MADE AND PRINTED IN GREAT BRITAIN
AT
THE CHAPEL RIVER PRESS, ANDOVER, HANTS
845

PREFACE TO THE TWELFTH EDITION

The urge to produce a new Edition of this book has been impelled by a sense of the importance of the study of Tropical Medicine to the British Empire in its great responsibility to its overseas possessions and their peoples—a responsibility which is now greater than ever, when this Commonwealth of Nations is emerging from the refining test of war. No effort has been spared to this end, and it is earnestly hoped that this 12th Edition may greet a new era and contribute in some small measure to the creation of a healthier and happier world.

Many chapters have been entirely rewritten and, as the occasion demands, special attention has been devoted to malaria, yellow fever and nutritional diseases. The chapter on rickettsiasis has been fully revised in order to keep pace with the kaleidoscopic changes which are apt to take place in this group; that on leprosy has been completely recast and modernized. To remedy many defects and omissions in the parasitological section, many illustrations have been redrawn, and the Editor has also endeavoured to bring the subject matter up to present day requirements. Special attention has been devoted to entomology in order to provide a rough guide to this intricate subject.

Other features are the inclusion of a chapter on the technique of injections, with special reference to blood transfusion in the tropics, and the insertion of a table of the main drugs in general use with their chemical composition, dosages and indications, which, it is hoped, may prove of real practical value to clinicians.

Many suggestions and criticisms for this Edition have been received from kind correspondents on both sides of the Atlantic. Each point raised has been rectified as far as possible. He is especially grateful for the practical assistance afforded him by Dr. C. Wilcocks, Acting-Director of the Bureau of Hygiene & Tropical Medicine, whose wide and accurate knowledge of the literature has been invaluable. Without the *Bulletins* issued under his direction the task of thorough revision must have been almost impossible. The late Director, Sir Harold Scott, with his critical eye, has also pointed out several errors and *lacunæ*. Dr. C. A. Hoare, of the Wellcome Research Institution, has generously suggested alterations in the protozoological section, and Dr. G. M. Vevers, of the Zoological Society of London, has supervised the zoological nomenclature. Other acknowledgments are made in the text.

It is hoped therefore that this Edition may prove of value to doctors and medical officers of the United Nations and that the reception afforded this manual throughout its long career may prove as favourable on this occasion.

> " Ring out old shapes of foul disease,
> Ring out the narrowing lust of gold ;
> Ring out the thousand wars of old,
> Ring in the thousand years of peace ! "
> (Tennyson. *In Memoriam, cvi, Stanza* 7).

PHILIP MANSON-BAHR.

149, *Harley Street, W.*1.

PREFACE TO THE FIRST EDITION

A MANUAL on the diseases of warm climates, of handy size, and yet giving adequate information, has long been a want; for the exigencies of travel and of tropical life are, as a rule, incompatible with big volumes and large libraries. This is the reason for the present work.

While it is hoped that the book may prove of practical service, it makes no pretension to being anything more than an introduction to the important department of medicine of which it treats; in no sense is it put forward as a complete treatise, or as being in this respect comparable to the more elaborate works by Davidson, Scheube, Rho, Laveran, Corre, Roux, and other systematic writers in the same field.

The author avails himself of this opportunity to acknowledge the valuable assistance he has received, in revising the text, from Dr. L. Westenra Sambon and Mr. David Rees, M.R.C.S., L.R.C.P., Superintendent, London School of Tropical Medicine. He would also acknowledge his great obligation to Mr. Richard Muir, Pathological Laboratory, Edinburgh University, for his care and skill in preparing the illustrations.

CONTENTS

PAGE

CHAP. 1. LIFE IN THE TROPICS 1
„ 2. LIFE IN THE TROPICS (*continued*) 17

SECTION 1.—FEVERS

Subsection A.—Fevers caused by Blood Protozoa

CHAP. 3. MALARIA 44
„ 4. HUMAN TRYPANOSOMIASIS 118
„ 5. LEISHMANIASIS 149

Subsection B.—Fevers caused by Blood Spirochætes and Spirilla

CHAP. 6. RELAPSING FEVERS 183
„ 7. LEPTOSPIROSIS 200
„ 8. RAT-BITE FEVER 210

Subsection C.—Fevers caused by Bartonella and Rickettsia bodies

CHAP. 9. BARTONELLOSIS (OROYA FEVER AND VERRUGA PERUANA) 214
„ 10. THE TYPHUS GROUP OF FEVERS. 220

Subsection D.—Fevers caused by Bacteria

CHAP. 11. PLAGUE 253
„ 12. TULARÆMIA 277
„ 13. MELIOIDOSIS 282
„ 14. THE UNDULANT FEVERS (BRUCELLOSIS) . . . 284
„ 15. ENTERIC FEVERS (AND BACTERIUM COLI INFECTIONS). 304

PAGE

Subsection E.—Diseases caused by Viruses

Preliminary Statement 321
Chap. 16. Yellow Fever 326
„ 17. Rift Valley Fever 349
„ 18. Psittacosis 352
„ 19. Rabies 356
„ 20. Dengue 366
„ 21. Phlebotomus Fever 373
„ 22. The Pock Diseases 378

Subsection F.—Fevers due to Atmospheric Causes

Chap. 23. Heat-stroke, Heat-exhaustion and Sun-stroke . 384

SECTION II.—VITAMIN DEFICIENCY DISEASES (AVITAMINOSES)

Preliminary Statement 394
Chap. 24. Beriberi 414
„ 25. Pellagra 433
„ 26. Scurvy in the Tropics 445

SECTION III.—ABDOMINAL DISEASES

Chap. 27. Cholera 448
„ 28. The Dysenteries and Liver Abscess . . . 465
„ 29. Tropical Sprue and Hill Diarrhœa . . . 529
„ 30. Infantile Cirrhosis of the Liver . . . 551

SECTION IV.—INFECTIVE GRANULOMATOUS DISEASES

Chap. 31. Leprosy 558
„ 32. Yaws (Frambœsia) 588
„ 33. Mycetoma and Blastomycosis 604

PAGE

SECTION V.—DISEASES OF THE CENTRAL NERVOUS SYSTEM

Chap. 34. Neurasthenia in the Tropics 613
„ 35. Encephalitis Japonica 617
„ 36. Lâtah, Running Amok and Koro 619

SECTION VI.—TROPICAL VENEREAL DISEASES

Chap. 37. Climatic Bubo (Lymphogranuloma inguinale) . 621
„ 38. Ulcerating Granuloma of the Pudenda . . 629

SECTION VII.—TROPICAL SKIN DISEASES

Chap. 39. Non-specific, Bacterial and Fungous Skin Diseases, etc. 636

SECTION VIII.—LOCAL DISEASES

Chap. 40. Tropical Pyomyositis—Rhinosporidiosis—Ainhum—Big Heel—Onyâlai—Chiufa 667

SECTION IX.—ANIMAL PARASITES AND ASSOCIATED DISEASES

Chap. 41. Parasites of the Circulatory System : Bilharziasis (Schistosomiasis) 676
„ 42. Parasites of the Lymphatic System and Connective Tissues : Filariasis 703
„ 43. Parasites of the Lung and Liver . . . 753
„ 44. Intestinal Parasites 759

SECTION X.—DISEASES DUE TO POISONS, INCLUDING SNAKE-BITE, AND INFECTION WITH DIPTEROUS FLIES AND LEECHES

Chap. 45. Vegetable Poisons 782
„ 46. Animal Poisons 790
„ 47. Myiasis and Leech Infection 802

SECTION XI.—TECHNIQUE

Chap. 48. Technique of Injections and Blood Transfusion 808
„ 49. Table of Drugs for Treatment of Tropical Diseases 818

APPENDIX

PAGE

Section A.—Medical Protozoology

PLASMODIIDÆ 840
THE SPIROCHÆTES 864
INTESTINAL AMŒBÆ 865
INTESTINAL FLAGELLATES 872
INTESTINAL COCCIDIA 875
BALANTIDIUM 877

MEDICAL HELMINTHOLOGY 879
 TREMATODES OR FLUKES 879
 THE BILHARZIA GROUP 887
 CESTODES OR TAPEWORMS 898
 NEMATODES OR ROUND-WORMS 908
 FILARIDÆ 924

MEDICAL ENTOMOLOGY 942
 ARACHNIDÆ (TICKS AND MITES) 942
 LINGUATULIDÆ 943
 TRUMBIDIIDÆ 945
 INSECTA 951
 PSYCHODIDÆ (SANDFLIES) 951
 CULICIDÆ (MOSQUITOES) 953
 MUSCIDÆ 978
 ANOPLURA (LICE) 990
 BUGS 991
 SIPHONAPTERA (FLEAS) 994

Section B.—Laboratory Methods

1. CLEANING SLIDES 998
2. METHODS OF PREPARATION OF BLOOD-FILMS 998
3. STAINING BLOOD-FILMS FOR BLOOD PROTOZOA AND DIFFERENTIAL COUNT OF CELLS 1000
4. VARIETIES OF BLOOD-CELLS AND THEIR SIGNIFICANCE 1002
5. BIOCHEMICAL METHODS OF EXAMINATION OF URINE AND BLOOD 1005
6. MICROSCOPICAL EXAMINATION OF THE FÆCES FOR EGGS OF INTESTINAL PARASITES 1006
7. SPECIAL STAINING METHODS 1012
8. DIAGNOSIS BY AGGLUTINATION 1014
9. PREPARATION OF SPECIAL CULTURE MEDIA 1017
10. METHODS OF PRESERVING HELMINTHS AND THEIR EGGS 1019
11. SCALES AND STANDARDS 1019

LIST OF PLATES

1. Sir Patrick Manson, G.C.M.G., F.R.S. . . . *Frontispiece*

Facing page

2. Malaria Parasites (*colour*). 50
3. The Blood Picture in Subtertian Malaria (*colour*) . . 51
4. Leishman-Donovan Bodies in Kala-azar (*colour*) . . 120
5. Tsetse Flies (*colour*) 121
6. Ticks (*colour*) 226
7. Rashes (*colour*) 227
8. Pellagra Rash on Feet 436
9. Pellagra (*colour*) 438
10. Intestinal Lesions in Amœbic and Bacillary Dysenteries (*colour*) 439
11. Microscopic Appearance of Cellular Exudate in Acute Bacillary Dysentery (*colour*) 470
12. Microscopic Appearance of Exudate in Amœbic Dysentery (*colour*) 471
13. Sigmoidoscopic Appearances of Rectum in Bacillary and Amœbic Dysenteries (*colour*) 480
14. Liver Abscess (*radiograph*) 506
15. Liver Abscess (*radiograph*) 507
16. Liver Abscess (*radiograph*) 513
17. Prepellagrous and Sprue Tongues (*colour*) . . . 535
18. Tinea Imbricata 656
19. Pinta 657
20. Bilharziasis of Bladder (*colour*) 677
21. Guinea Worm (*radiograph*) 750
22. Calcified Cysticerci in the Thigh (*radiograph*) . . . 751
23. Human Intestinal Protozoa (*colour*) 864
24. Human Intestinal Protozoa (stained with Weigert's solution) (*colour*) 865
25. Normal and Abnormal Blood-cells (*colour*) . . . 1002
26. Eggs of the Commoner Helminths found in man (*colour*) . 1003

LIST OF MAPS

MAP

1. Distribution of Human Trypanosomiasis 118
2. Equatorial Africa, showing distribution of African Sleeping Sickness. *Follows Map* 1
3. Distribution of Leishmaniasis 150
4. Distribution of Yellow Fever 326
5. Distribution of Bilharziasis 676
6. Distribution of Filariasis 703

TROPICAL DISEASES

CHAPTER I

LIFE IN THE TROPICS

GENERAL OBSERVATIONS

It is difficult to define in exact terms what is meant by " a complete method of assessment of fitness for life in the tropics." There should be an attempt to sum up the individual in all aspects, not only fitness of body and internal organs to withstand the strain of tropical conditions, but also of the nervous system to remain stable and serene in the face of privations and petty provocations.

The best kind of **mind** for tropical life is an enquiring one : one which takes an interest in the people and things around ; in fact the type of person best fitted for this kind of existence is one who has a passion for hobbies of all sorts.

In the assessment of mental suitability, it is important to survey the applicant's antecedents in all their bearings. Thus, it is essential to enquire into family, upbringing, school and University careers, the idea being to discover, not so much the scholarly and athletic prowess of the candidate, as his general bearing towards his fellows, and to reveal the existence of complexes and fads which would militate against success abroad. The tropics is no place for the highly-strung or neurotic. With young men the question of alcohol consumption, excessive smoking and other deleterious habits must inevitably be raised. This, naturally, is often a delicate matter, but it is so vitally important that even a suspicion of excess unfits the candidate for tropical service,since what might constitute a minor evil in civil life in temperate zones may be a vice under the more exacting conditions of the tropics. This does not mean that the strict teetotaller is any more fitted than the heavy drinker. The emphasis is on moderation and self-control.

The **age** of the candidate is obviously important, and on this there is general agreement. He or she should have attained maximum development before going out. Those under twenty-one—and this is true especially of women—withstand extreme heat and humidity badly, and appear, moreover, to be more susceptible to tropical diseases. Women should be fully matured in mind as well as in body and, as a rule, their age should be somewhat higher than that for men, which is from twenty-three to twenty-five. It is a matter of observation that men over forty find it very difficult to accustom themselves to intense heat, though exceptions will readily occur to the mind, such as Robert Koch, a pioneer in medical science, and Abel Chapman in zoology. Both had already passed forty ere they set foot in Central Africa, and both found themselves equal to its exacting demands.

While there can be no absolute standard of **height and weight**, the deviation from the generally accepted averages should not be great.

As a rule, spareness is more desirable than plumpness. Certainly the tropics is no place for the fat man. The " lanky," spare type is best suited to tropical conditions, and the dark-haired, brown-eyed and dark-complexioned is generally considered more fitted than the blue-eyed, fair-haired, tender-skinned " Norse " or " Aryan " type. It is generally assumed that the brunette southern type with increased pigmentation of the skin is thus endowed as a protection against heat but, here again, there are exceptions to the rule.

Teeth.—As the food in the tropics is neither so palatable nor so easily masticated as at home, teeth must reach a high standard, and candidates with universally carious teeth or incomplete dentine should be eliminated. Everyone who proposes to go to the tropics should have his mouth put in order, because dental decay takes place more rapidly in intense heat. There cannot be any objection to dentures if the owner possesses a spare set, and they are adequate and comfortable.

Nose and throat.—Special care should be directed to the tonsils. If they are enlarged and septic they must be enucleated. Subjects of post-nasal catarrh and chronic granular pharyngitis do not do well. Sinus trouble does not improve in the tropics and, for North and West Africa, where sandstorms are common, persons suffering from chronic antral disease should be refused.

Eyes and ears.—Reasonable visual acuity is essential. Opinions differ considerably on the extent of deficiency which may be passed over. The Editor is of the opinion that grave refractive errors are deleterious and, in certain circumstances, candidates with a degree of myopia about — 6D should be rejected. No candidate with high myopia is suited for a bush or isolated station. If glasses must be worn, the wearer must have spare sets. Crookes's lemon-tinted lenses are of value in diminishing glare. In certain regions in the Sudan and Northern Nigeria, for instance, smoked glasses are a necessity to mitigate eye-strain. Normal colour vision is essential. Chronic conjunctivitis of all kinds is a distinct disability.

Middle-ear disease with discharge and aural eczema disqualify: both are made worse by tropical conditions. Perforation of the tympanum and any kind of deafness must be investigated. Deafness in more than a moderate degree is a bar.

Respiratory system.—Special attention must be paid to the lungs. Asthmatics and subjects of " hay fever " are quite unsuited for tropical residence, for, contrary to popular belief, asthma, hay fever, allergic rhinitis and, indeed, allergic conditions of all kinds are aggravated by the luxuriant vegetation, while flowering grasses and the pollen of rice and sugar-cane are very irritating. Sugar-cane fibre is often used for stuffing pillows and causes asthma in susceptible individuals. The same applies to chronic bronchitis and emphysema. Any suspicion of tuberculosis, whether glandular or parenchymatous, calls for X-ray examination, especially in candidates with a bad family history.

The Editor is strongly of the opinion that any candidate with Ghon's focus, or any evidence of healed apical lesions, is quite unfitted for the tropics. Contrary to popular opinion, damp heat induces and fosters but does not cure tuberculosis. Those who have calcified bronchial glands, and who have already thereby demonstrated their resistance to the disease, may, on the other hand, be considered suitable.

Cardiovascular system.—Any valvular heart disease is a contra-indication. It is probably true that persons with mild degrees of mitral stenosis are not seriously inconvenienced by tropical life, but the increase in the metabolic rate and the strain placed upon the heart and respiratory organs by extreme heat has a deleterious effect upon the action of the heart. Of all heart lesions, *aortic regurgitation*, especially of luetic origin, is the most undesirable. Sinus arrythmia and extrasystoles are frequently encountered in tropical residents, and are not in themselves deleterious. Persistent tachycardia, from whatever cause, should be a bar to tropical service, and a candidate exhibiting a rapid pulse, which does not arise from nervousness during the medical examination, should be subjected to a searching exercise tolerance test.

Hyperpiesia.—Subjects of high blood-pressure are definitely excluded. Hyperpiesia, due to intrinsic hypertension or arterio-sclerosis, is a serious handicap in the tropics. Often, in nervous young men, a high systolic reading may be obtained, and while this for the most part can be overlooked, a persistent high diastolic pressure above 100 mm. Hg is an absolute disqualification. Such persons inevitably break down after prolonged tropical residence ; they are more liable to neurasthenic symptoms, and, in the Editor's experience, usually end up with cerebral hæmorrhage.

Digestive system.—Nothing is more important than the digestive history. The organs of digestion are necessarily subjected to considerable strain ; therefore subjects of nervous dyspepsia, hyperchlorhydria, or severe gastric disturbances, should not go abroad. A previous history of duodenal or gastric ulcer, especially where confirmed by radioscopy, should debar a candidate, especially from places characterized by damp heat, such as the west coast of Africa or Malaya. It must be remembered always that, even under the best circumstances, a great deal of the daily fare consists of frozen or tinned food.

If the indigestion is due to chronic inflammation of the *appendix*, it is most important that appendicectomy be performed before sailing. It is obvious that, for many reasons, appendicitis may be a much more dramatic and important event than in more highly civilized conditions.

Persons of a " bilious " or a hepatic tendency, with lustreless skin and a jaundiced look, withstand the tropics badly ; therefore any palpable enlargement of the *liver* must be noted. *Splenomegaly* may, occasionally, denote previous attacks of malaria, and indicate that the candidate is hypersensitive to this infection or, on the other hand, it may mean that he has some obscure blood disease, and is therefore unsuitable.

Sufferers from chronic colitis are ruled out. A history is not always easy to obtain ; but if there is any previous history of blood or mucus in the stools, or both, or pain on defæcation, or any suspicion of ulcerative colitis, the matter must be investigated. This disease is so liable to remissions that the candidate may appear well and healthy at the examination, but relapses under tropical conditions are apt to be especially severe. The peculiarly sensitive type of person who is colon-minded, and subject to mucous colitis and spastic colon, does badly and cannot be recommended.

Subjects of diverticulitis fare badly also, and, if this condition is detected as a cause of abdominal discomfort in a more elderly subject, tropical service is not recommended. Any history of gall-bladder disease should debar the candidate, owing to the risk of developing cholecystitis and biliary calculus under tropical conditions.

Hæmorrhoids.—Piles are a curse of life in hot climates where those predisposed to the disorder almost invariably become sufferers. Piles should be removed surgically, as injection methods do not appear to be altogether satisfactory.

Hernia.—Candidates with inguinal herniæ of any description must submit to operation before going abroad. Trusses, even of the lightest variety (celluloid), are most inconvenient, and are apt to cause intertrigo and skin irritation. The same applies to umbilical herniæ ; pads cannot be worn and are usually inefficient.

Genito-urinary system.—Renal and vesical calculi are more likely to develop in the tropics than in temperate regions. No one with a history of renal colic should be accepted. Enlarged and palpable kidneys may mean congenital cystic disease, which is a disqualification. Special attention must be paid to the urine. Moderate degrees of albuminuria (physiological or postural) are extremely common in athletic and otherwise healthy young men, and the Editor is of the opinion that it is quite unfair to reject a suitable candidate merely on this account. It is different when there is an appreciable amount of albumin (5 per cent.). Numbers of casts in the deposit indicate a predisposition to severe renal disease. Sugar in the urine, however, is somewhat different. If a very considerable precipitate is obtained with Fehling's and Benedict's solutions, then a blood-sugar curve estimation must be done. No diabetic ought to be passed for service in the tropics. Opinions vary about renal glycosuria. If the candidate has a low sugar tolerance with a low renal threshold for glucose, he is best out of the tropics, as the condition may possibly predispose to true diabetes.

The cellular deposits of the urine should always be examined. Subjects of phosphaturia, so-called "*phosphatic diabetes*," owing to the concentration of urine which occurs in a hot climate, are unsuitable. Those showing evidence of *Bact. coli* or streptococcal infection must be rejected. A constant source of trouble is urinary tuberculosis, on account of the difficulty of detecting the tubercle bacillus ; but when large numbers of pus cells are present in the urinary deposit without other ascertainable cause, tuberculosis should be suspected and the candidate rejected. Chronic gonorrhœa and chronic prostatitis are always a source of trouble and a reason for rejection.

Female candidates.—Among women, disorders of the genital organs tend to dominate the picture. Since impairment of the menstrual functions is usually aggravated by tropical residence, the menstrual history must be carefully investigated. Those inclined to dysmenorrhœa or menorrhagia should be forbidden, if possible, to go out. Subjects of periodic amenorrhœa suffer more in the tropics, and the same may be said of uterine displacements. Women who are predisposed to miscarriage are more liable to this accident under the less civilized conditions of the tropics.

Minor vaginal or uterine disabilities, such as vaginal discharges, may be overlooked. Women in advanced pregnancy should not attempt to go out, and it is advisable that a primipara should not proceed to a hot climate in the middle of her pregnancy.

Integuments.—Special attention must be paid to the skin, hair and nails. *Alopecia* is apt to progress under tropical conditions. *Cracked* and *brittle nails* indicate a feeble constitution. *Clubbed fingers* may indicate cardio-pulmonary disease, or may be merely a congenital deformity. Anyone with an abnormal *skin* must be specially investigated. It must always be borne in mind that the skin, as an organ of elimination and metabolism, is much more important in tropical than in temperate countries. Subjects of deficient sweating (anidrosis), unable to sweat freely, not only suffer acute discomfort but are in danger from heat stroke and heat exhaustion. Therefore, candidates having dry skins (xeroderma) and ichthyosis must be rejected. On the other hand, individuals whose sweat-glands are abnormally active do well.

Septic spots on the skin of the back and chest are frequently encountered in young men and, though each case should be judged on its merits, it must be remembered that residents in most tropical countries, but especially in West Africa, are particularly liable to septic infections, especially boils, so that anyone who is specially susceptible to the staphylococcus should be considered unsuitable.

Psoriasis is always a difficulty. Milder degrees may be passed over, and as a general rule are apt to disappear in very hot countries. Extensive psoriasis, however, especially when associated with suppuration, should debar from the tropics.

Acne.—Acne is improved by heat; many healthy and vigorous individuals are marred by this complaint, and they should be permitted to go abroad.

Eczema of all kinds is a distinct disability and so are sensitive (allergic) skins, and those liable to intertrigo.

Central nervous system.—Nervous control is of paramount importance in the tropics. All exhibiting neurotic and hysterical tendencies should be rejected. *Epilepsy* is not always easy to detect, but epileptics must on no account go out. Any chronic affection of the spinal cord, e.g., Friedreich's ataxia or spastic paraplegia, is a disqualification, as is a previous history of encephalitis lethargica or cerebro-spinal meningitis.

A candidate has sometimes suffered from infantile paralysis. If it merely affects one limb, and the muscular atrophy is not too extreme, he may be passed, though it must be understood that the tropics is no place for a cripple. Exaggerated deep reflexes and tremors of hands or tongue denote that the candidate has an unstable nervous control, and that he is unsuitable.

Anæmia.—Persons with anæmia which cannot be adequately explained are usually in poor health; they are "below par," and this succinctly suggests that they are lacking in vigour, energy and initiative. The pale young man or the sallow woman is unsuited for tropical residence. The
content is probably more important from this point of view
the red-cell count. Secondary anæmia usually indicates some
condition. It may be digestive, pulmonary, or even cardiac.

Pale faces become paler still in the tropics, and the condition is more likely to progress there.

Affections of the thyroid.—The possibility of hyperactivity or insufficiency of the thyroid gland has to be kept in mind. The Editor is convinced that all thyroid tumours, whether adenomata, cystic adenomata or thyroid hypertrophy, are definite contra-indications to tropical service. The form of hyperthyroidism (usually due to substernal thyroid) which, though not leading to exophthalmic goitre, yet produces thyrotoxicosis with a special strain on the cardiac muscle, is particularly to be feared. The thyrotoxic heart is produced by exposure to tropical conditions, and may progress unchecked and end fatally. All degrees of hypothyroidism are also unsuited to tropical conditions.

Other endocrine disorders.—Endocrine disorders, such as hyperpituitarism, hypopituitarism, "Fröhlich's syndrome," achondroplasia, and developmental anomalies, are to be excluded.

Gout and rheumatic arthritis.—A gouty diathesis is occasionally seen in comparatively young people, and may manifest itself in many ways. Gout may actually be provoked or aggravated by tropical conditions, and therefore must be regarded as a contra-indication. There is a popular idea that rheumatic affections of the joints are improved by exposure to heat, but this is far from true. Usually they are aggravated. The same is true of fibrositis.

Other disabilities.—Even such minor blemishes as the state of the feet must be inquired into. Deformities, club foot and hammer toes, in those who may be called upon to undertake long marches, may be held to be distinct disabilities. Fungus infection of the feet is particularly intractable under tropical conditions.

Preparations before sailing.—All those who are proceeding to the tropics and subtropics, whenever they come into contact with native servants, and whenever they mix with the native population, or whenever they are forced to live in less sanitary surroundings than they have been accustomed to, should be inoculated about four weeks before departure against typhoid and paratyphoid (T.A.B.) (*see* p. 316). They should also be revaccinated, if this has not been done within the three previous years. Very often this vaccination may not cause any obvious reaction, or in popular language, may not "take," but it must be attempted none the less. The vaccination may be conveniently performed at the same time as the second inoculation. If for other reasons, such as business matters or preparing for departure, circumstances prevent this, both inoculation and vaccination can be given on board ship if the voyage is long enough, e.g., the journey to India. Allowance must be made for any possible reaction. Thereafter it should be the rule to repeat the vaccination every five years and the inoculations every three years. Those proceeding to the West Coast or other parts of Africa, and to South America, where yellow fever is endemic, are strongly urged to be inoculated against this disease (*see* p. 346). It must be emphasized that out of the thousands who have now been protected only a few have contracted yellow fever.

Some people have an idiosyncrasy to quinine; these, if they are going to regions where quinine prophylaxis is practised, should accustom themselves to the drug by taking a trial on board ship. In view of the increasing importance of atebrin (mepacrine) malaria prophylaxis they should do the same with this drug.

PASSING PATIENTS FIT TO RETURN TO THE TROPICS AFTER LEAVE

Great care should be taken over the " passing-out " examination before return to duty from leave, especially in those who have suffered from nervous debility, with insomnia and associated psychological disturbances. In these cases a full period of leave must be granted for recuperation. The mind must be serene, the reflexes normal, and the patient should eagerly anticipate his return, and not recoil from the very idea. Those who have had malaria should have fully recovered ; the spleen should no longer be palpable, and the blood should reach normal standard. Should blackwater fever have supervened, and should it be an isolated attack, and recovery be complete, the patient may return ; but if he has suffered from more than one attack and has survived, it is extremely dangerous to risk a third (*see* pp. 90, 108).

Trypanosomiasis and kala-azar, formerly so greatly feared, are now amenable to treatment and cure by specific drugs, and the cure is so dramatic and complete that provided there has been a suitable period for convalescence, no valid objection can be urged against a return to duty.

Relapsing-fever cases are generally completely cured of their infection on arrival in this country, and if no disability remains they are suitable for return. In the tropical typhus and undulant fever groups, victims of which are seen comparatively often, recovery is generally quite complete, and no physical disability remains. In the latter, however, a sufficient period of leave must be granted for full convalescence.

Other tropical infections to which special attention should be given are the dysenteric group. Amœbiasis formerly caused considerable apprehension, because of the absence of a final test of cure. It is true that incompletely cured patients, and those who harbour cysts in their stools, are more liable to relapse under tropical conditions than those who continue to reside in temperate climates. Therefore, all those who have suffered from clinical dysentery during their period of service should be specially examined on their return. Their stools should be tested for amœbic cysts, and a sigmoidoscopic examination performed if necessary. There is no objection whatever to the return of amœbiasis patients, provided they have undergone a thorough course of anti-amœbic treatment. Those who have suffered from bacillary dysentery—and they are much more numerous than is generally thought—usually make a complete recovery on return to England, and relapses are not to be anticipated. The form known as chronic bacillary dysentery is much more refractory, but can now be cured by sulphaguanidine.

Another important form of tropical diarrhœa is sprue (*see* p. 529). There is always considerable hesitation in permitting these patients to to the tropics, especially to the locality where the disease was first contracted. It is undoubtedly true that relapses are more likely in the tropics. Probably complete recovery occurs in people under forty years of age, and, if they have been quite free from all symptoms and signs for one year at least, then a return to the tropics may be sanctioned.

Ancylostomiasis and other worm infections not infrequently cause loss of vigour and ill-health in those returning from leave. The possibility of an ancylostome infection must always be borne in mind as the cause of cachexia and fatiguability, especially in women who have been residing on tea estates and other plantations. Their stools must be examined by concentration methods (*see* p. 1008). After adequate treatment they are fit to return.

Postoperative Debility

The date of return after operation is always debatable, especially in operations on the gastro-intestinal tract. Appendicectomy, and even cholecystectomy, are quite simple and give rise to little difficulty, but in more elaborate operations, such as gastro-enterostomy for duodenal ulcer or pyloric stenosis, circumspection is needed. The Editor is very chary of permitting such patients to return to adverse tropical conditions, unless the operation has been a distinct success, the condition is excellent, and the digestion perfect.

The same general rule should be applied to operations on the genito-urinary tract. Renal calculi are common in the tropics, and certain individuals seem predisposed to them. If nephrectomy has been performed for renal calculus, and the patient is in a good state with one functioning kidney, there is no objection to return to the tropics, provided that it is not a hyperendemic malarial zone. To a person with one kidney, an attack of malaria or blackwater fever may become a matter of life and death.

ACCLIMATIZATION

Obviously transportation to the tropics, where the isotherm may be anything from 20–30° F. above that previously experienced, subjects the body to considerable strain and to consequent alterations in metabolism. It is also a matter of common knowledge that individuals vary to a very great degree in their reactions to heat. Most people show temporary reactions which may be regarded as adaptations to climatic thermal changes.

The saying " What is one man's meat is another man's poison " also applies to climate ; but instinctive dread of extreme degrees of heat and humidity is rapidly diminishing as communications are being opened up by air travel. The aeroplane, the motor car and the refrigerator have robbed many places of most of their terrors, and the West Coast of Africa is no longer the White Man's Grave. It is common knowledge that some individuals, who as likely as not are of indifferent physique, thrive in the tropics ; some, for instance, prefer to live in Central Africa, though these are quite exceptional.

Within a relatively short space of time a pure European tropical population has arisen. In the British Empire there are such communities in

India, Ceylon, Burma, Queensland, and the highlands of Kenya. It may therefore be asked: Can the European preserve his identity, maintain his vigour, energy and culture; can he in fact hold on to whatever is held dear in European civilization under the stress of tropical conditions? Cilento remarks of the tropical-born Australian that the race is in a transition stage and there is now being evolved a distinctive tropical type adapted to life in the environment in which it is set.

It is evident that climate can produce profound alterations in physical characters in a comparatively short time. Many striking examples of adaptation could be quoted. Thus, Gorgas has cited the large-scale experiment of Panama, where for ten years Americans, including men, women and children, mostly doing hard manual labour, exposed to all kinds of weather conditions, remained in good health. The European inhabitants of the West Indies, Barbados, Jamaica, St. Kitt's, Antigua and the islands of St. Martin and Curaçao, are the descendants of white settlers and are to be found to-day, healthy and vigorous. The German colony of Espirito Santo, in Brazil, which was founded in 1847, is now in a flourishing condition, with a birth- and death-rate comparable with that of Europe.

There is also the oft-quoted unintentional experiment which took place in the Dutch East Indies 289 years ago. In 1655, eight Dutch soldiers were sent by the Netherlands East India Company to the little island of Kissa, 16 miles off Timor. It appears that this lonely outpost was quite forgotten, and the men soon realized that they had been marooned. They had their wives with them, so they built houses and cultivated the land. They have been wonderfully fertile and now number over 300, and are a sturdy race, with no signs of ill-effects from inbreeding. Many have European fair faces and complexions, light hair and blue eyes. The example of the Dutch Island of Saba is also quoted by Bagshawe. This lies near St. Kitt's and, for 250 years, an English-speaking white community, without racial admixture, has existed and multiplied, though it is now declining under the stress of economic circumstances. Price, in 1984, writing of this community, concluded that cold-temperate zone whites can retain a fair standard for generations in the trade-wind tropics, provided that the location is free from the worst forms of tropical disease, and that the economic return is adequate. Whatever may be the ultimate truth of this matter, it is not only advisable, it is necessary, to send European children, at six or seven years of age, to a temperate climate to be educated. With few exceptions, serious harm results from keeping white children too long in the tropics, though European infants up to four or five years, it is true, thrive in most tropical climates with the exception of the West Coast of Africa.

After prolonged residence in tropical highlands, especially those of East Africa, nervous changes are specially apt to develop. It is possible that many of the nervous symptoms attributed to climate and altitude may be the result of isolation and other social influences inherent in residence in some tropical countries. While exceptional examples of the survival of the European race in some tropical, though mainly insular climates, exist, the general opinion is that, whenever it has been attempted on a considerable scale, the second and third generations show departures from type, suggesting that prolonged residence in the tropics is capable of altering the racial type.

TROPICAL CLIMATES

According to Supan's classification the following are the main types of climate:—

Tropical or warm climates.—Tropical climates extend from the equator to the mean annual isotherm of 20° C. The northern limit is situated at 35° of north latitude; the southern at rather less than 30° southern latitude. The true tropical zone is divided from the subtropical by a purely arbitrary line which represents the isotherm of 20° C. for the *colder months* of the year in both northern and southern latitudes. The tropical zone corresponds roughly to 23½° N. and S. latitude, being more or less confined to the tropics of Cancer and Capricorn.

The *subtropical zone* lies between the isotherm of 20° C. (68° F.), for the temperature of the coldest month, and the same for the mean temperature of the year. This includes a portion of North America and a considerable portion of South America, Africa, Asia Minor, Persia, North India, China and Australia.

In the tropics there are four divisions of warm climates, viz., the equatorial, the trade-wind, the monsoon belt and the mountain climates.

The equatorial belt.—Those localities within a few degrees of the equator are always subject to rain and cloud, because the hot air is charged with aqueous vapour from the sea. This belt is subject to alternate seasons of wind and calm, e.g., in January to the north-east trade winds, and in July to the south-east trades. Such places are Southern India, Ceylon, Java, Colombia, South America, parts of the Nile Valley, and the Gold Coast.

Trade-wind belts.—The lands which lie outside the boundaries of the equatorial or rain belt, situated some 20° to 35° N. or S. latitude, are among the driest of the world, except in India, where the south-west monsoon brings a little rain into the dry regions of the Punjab and Sind. These places are the dry zones of California, and other parts of North America, the Sahara and Nubian Deserts, parts of Arabia and Persia, Argentine, South-West Africa and the interior of Australia.

Monsoon belts.—The monsoons are classifiable into:—north-east, south-west, north-west, south-east, and west monsoons.

The *north-east* and *south-west* monsoons are met in the Indian Ocean and on its coasts. The interval between these two monsoons is characterized by changeable winds, which blow alternately in opposite directions—north-east and south-west. The latter prevails in May, June, July and August; the north-east, which is due to the cooling of the plains, is really a trade wind, and blows in November, December, January, February and March. On the south-west monsoon southern India largely depends for rain.

North-west and south-east monsoons are found in the southern hemisphere, especially in Australia.

The *west monsoon* is a south-westerly wind along the coast of Africa, from the Cape Verde islands down to Walfisch Bay.

Climates.—The effect of elevation is to lower the temperature. This is due partly to the expansion of the air, partly to the lessened amount of earth to radiate *black heat* (that which is absorbed by the rocks and soil), and partly to the movement of the wind. The greatest blessing of these elevations in the tropics is that they provide cool hill stations to which resort may be had during the hottest months, and where the climate simulates perpetual spring.

The main factor is the sun's rays, which in tropical climates are vertical and thus penetrate to a degree unknown in temperate zones; at the zenith they are fifteen times stronger than when the sun stands 10° above the horizon. There are two other climatic factors which act adversely: the humidity of the air, which is usually much higher than any experienced in Europe, and the air currents. Apart from these, the main disturbing factor to the newcomer is the small daily variation in the temperature, which seldom falls below 68° F.; in vain he longs for the coolness of the twilight. The evenness of the tropical climate, so different from the extremes in which the European has been brought up, does not lead to alleviation of existence, but to the very opposite. The lack of daily variations between night and day, winter and summer, becomes monotonous and deprives the European of the stimulus to which he has been accustomed. This is paralleled by the everlasting twelve hours of darkness succeeded by twelve hours of light. The low-lying tropics usually have an isotherm of 78° F. compared with that of Central Europe of 48° F., but for every 300 feet of elevation above sea-level the temperature is reduced by 1° F.

It must not be thought that the geographical torrid zone necessarily embraces all the true tropics. The highest isotherm lies some 10° north of the geographical equator, and north and south of this line is an isotherm of 20° C. (68° F.), and even within this warm zone there is a subdivision where, in the cooler months, the temperature never falls below 68° F.

Three factors must be considered in any tropical climates; these are the humidity of the air (the wet-bulb temperature which usually reaches a figure of over 80-90 per cent.); the actual temperature; and the air currents. Thus, it is not right to speak of a "tropical climate" as a complete entity, for there are minor variations to be found within the tropics themselves.

Humidity is a decisive factor in climatology. Thus, warm air contains more moisture than cold, and, when cooled, a point of precipitation is reached; this is known as the "dewpoint."

Absolute humidity is the actual amount of vapour present in air, expressed in terms of weight and pressure. This remains a constant factor unless influenced by evaporation or precipitation, and it reaches its maximum expression in the equatorial zone.

Relative humidity is the percentage of vapour present in the air of the total amount possible in complete saturation. It is measured by the differences between the wet and dry bulb thermometers.

Saturation deficiency is the difference between the absolute humidity and the amount that air at the same temperature could contain if saturated. The greater the difference the more rapid is evaporation from the skin and consequent cooling of the body. Saturation deficiency tends to be high in the dry hot season, but to decrease with the fall of rain. These are important factors, because temperature and humidity govern the mosquito and the malaria parasite (see p. 46).

Within the tropics will be found every intergradation between a marine and a continental climate, with very considerable seasonal variations on tropical seaboards and in tropical islands. Thus, in the Antilles and in the Pacific, variations of 30° F. are the rule, while inland, in the centre of the African continent, these variations may be as high as 64° F. Naturally, the amount of rainfall and the duration of the season exert a considerable influence upon the temperature and humidity.

In India, the Far East and other parts of the tropics, the rainy season is known as the *monsoon*, so that there are considerable temperature variations during the dry and wet seasons.

In the northern summer, portions of the Asiatic continent become over-heated, and in the southern summer the Australian and African continents become similarly hot, and thereby air currents are initiated, which are known as the south-west monsoons of India and East Africa, the north-west monsoons of Australia, and the north-east monsoons of East Africa; in the regions lying between these there are minor intergradations of these major winds.

The summer monsoons are invariably sea winds, which bring rain and overcast cloudy weather and, if they blow from a cooling sea, cause a drop in temperature. The winter monsoons, on the other hand, are land winds, and are accompanied by hot, dry weather and a rise of temperature; the relative dryness is determined by the character of the continent from which they come.

Sea currents to a certain extent influence tropical climates. Thus, the cold antarctic current considerably cools the air on the west coast of South America, where the coastline comes into contact with the Antarctic or Humbold current, and this exerts a considerable effect upon the rainfall, which may be, as in Chile and Peru, practically non-existent. The barometric pressure is, on the average, considerably lower than in temperate zones, but its influence upon human well-being is not completely understood.

The regulation of heat.—A given area of a portion of the tropics receives the same number of rays from the sun as any other place on a line drawn round the globe in the same latitude, but atmospheric heat is not derived directly from the sun's rays so much as from the *black heat* which is radiated from the land and sea. The rays from the sun heat the earth first, the process being known as *insolation*. This heat has little power on land, and its effect is sensibly diminished even twenty feet above the surface of the earth. The earth is surrounded by a gas envelope, or *atmosphere*, the density of which is equal to a pressure at sea-level of 15 lb. to the square inch, becoming less dense the farther away from that level. This atmosphere absorbs a large proportion of the rays which strike its outer limit; hence the sun's rays, which travel obliquely in the temperate zone, traverse a thicker layer than the rays which travel *vertically* in the tropics. In this way in the non-tropical regions radiation is absorbed by the intervening atmosphere and the power of the sun correspondingly diminished.

PHYSIOLOGICAL EFFECTS OF A HOT CLIMATE

Observations have been made on the effects of tropical climates on body temperature, skin reaction, respiratory exchange, urinary excretion and the blood, with conclusions on the influence upon digestion, circulation, nervous system, generative organs and growth.

Body temperature.—On passing from a temperate to a tropical climate, a slight rise in body temperature occurs, rarely exceeding 1.5° F., and, after arrival in the tropics, the body temperature of the newcomer remains slightly elevated. In fully acclimatized Europeans it settles down to normal, but tends to rise after severe exercise. Breinl found the rectal temperature to be 101° F. (38.3° C.) on really hot days.

Low fever.—Low fever is the term given to a little understood clinical picture, which is known by this vague description all over the world. It is characterized by lassitude, debility, and a long-drawn-out slight rise of temperature, which is frequently seen in children. Very little has been written about this condition in textbooks, but all are agreed that, in spite of the most searching bacteriological and biochemical tests, no specific organism can be held responsible. If low fever cannot be assigned to latent malaria, amœbiasis, closed tuberculosis or gonorrhœal prostatitis, then it is certainly due to climatic causes, and probably " climatic fever " would be a better term. Most people become acclimatized to heat, but there are some whose heat-regulating mechanism cannot adjust itself fully ; it is in these that climatic fever is seen. The temperature seldom rises above 100° F. at the hottest period of the day ; but the most noticeable feature is that the daily minimum is raised the same amount as the maximum. *The daily variations remain the same as before, but the entire level is shifted upwards.* Some of these patients feel chilly at times, and during these spells are most uncomfortable. Occasionally, too, there are spells of excessive sweating.

Skin reaction.—The regulation of body temperature is effected by evaporation of water from the surface of the body and from the lungs. It has been shown on a white skin that the temperature falls with the appearance of perspiration, and the greater the degree of perspiration the greater the fall of temperature. A brown or black skin absorbs more heat than the white skin, and the point where perspiration shows itself is reached earlier in the brown-skinned, showing that their cutaneous heat-regulating apparatus is more sensitive than that of the white man. In especially sensitive skins a particularly irritating form of urticaria—solar urticaria—has been described.

Respiratory exchange.—The cooling process is brought about by evaporation of water from the lungs. This is also to some extent effected by the attraction of the blood to the surface of the body. The place of the blood thus transposed is taken by air, and this is one of the reasons why the lungs weigh less in hot than in cold or temperate climates. The lung capacity is increased, and thereby the respiratory rate lowered.

Urinary excretion.—The excretion of urine is diminished with excessive sweating. The daily output of a normal adult in the tropics is 500–600 c.c., as against 1,500 c.c. in temperate countries. The urine is concentrated, but apparently contains the same amount of waste material as that found in 1,500 c.c.

Blood.—Investigations made in Java, the Philippines, Queensland, West Africa and Iraq indicate that climate alone produces no change in the formed blood elements, except a shift of the Arneth index to the left (*see* p. 1004). Nor does it produce any change in the hæmoglobin content or the specific gravity of the blood. De Langen and Schut in Java asserted that in the newly-arrived European the blood sugar is augmented ; or, at any rate, there is a rise in the fasting level. On the other hand, Sundstroem concluded that the endocrine glands in the tropics exhibit a decrease of functional activity and that, therefore, a parallel decrease in blood sugar should take place. He found this in European individuals of both sexes who had lived in the tropics since birth. A positive correlation, moreover, was found to hold between the sugar values and the lecithin and cholesterol ratios of the blood.

The non-protein nitrogen, on the other hand, was about 25 per cent. higher than the standard average, but the urea, uric acid and total creatinin were normal. It is thought that endogenous and exogenous toxic substances, usually excreted by the kidneys, may be retained, and possibly predispose to the greater susceptibility to nephritis in a tropical climate.

The phosphorus content of the whole blood was found by Sundstroem to be normal in individuals who had spent less than one year on the tropics, after which it dropped to 9 mgm. per 100 c.c. for men, and 7 mgm. for women. Various suppositions are advanced to explain the diminution of blood phosphorus in the tropics. It is thought that a climatic stimulus may temporarily throw an excessive load on the mechanisms which supply phosphorized material for anabolic processes. The content of total fatty acids in the blood of tropical residents appears to be considerably lower than the available standard figures for cooler climates, and this is thought by de Langen to explain the rarity of gall-stones in Malays and Javanese.

Digestion.—At first, as every traveller will testify from experience, there is a stimulation of appetite, as well as of the digestive function, but this is a passing phase, and is soon replaced by a diminution of appetite and a lowering of the digestive capacity, together with a diminished desire for animal food. Diarrhœa and loose stools, probably of bacterial origin, are almost invariable on first exposure to tropical conditions, and are soon followed by constipation.

Circulation.—Exercise and humid heat produce a rise in blood-pressure, and also in the pulse-rate (Breinl). The average systolic blood-pressure shows a tendency to fall concomitantly with profuse sweating. The diastolic pressure closely follows the systolic.

Nervous system.—On the nervous system the first effects are those of stimulation, followed by depression, and when the latter is prolonged a neurasthenic state with loss of memory (" West Coast memory ") is produced. In tropical residents of long standing there is an exaggeration of the deep reflexes, tachycardia and, eventually, insomnia and abnormal reaction to stimuli, which indicate a loss of control by the higher centres, and result often in unreasonable mental irritability. Electrical conditions also powerfully affect the nervous system. Among European children, especially, the whole nervous system appears to be in unstable equilibrium, resulting in fretfulness, peevishness and often in frank hysteria.

Generative functions.—In both sexes there is at first a stimulation of the sexual libido, but excess is soon followed by exhaustion, and often by sexual neurasthenia. In children, puberty is attained at an earlier age, so that in European girls menstruation commences about a year earlier than in temperate climates, but the onset of the menopause is not retarded.

Growth.—Growth in children is rapid, and the children are usually under weight and lacking in physical strength. European children brought up in the tropics are generally described as " weedy."

Acid-base equilibrium and basal metabolism.—Sundstroem and Radsma are the only authorities who have carried out much work on these problems. The former finds that, as a rule, the alveolar carbon dioxide tension is lowered in the tropics. An alkalosis is present in the majority of tropical residents at the height of the hot season, and may have an undesirable effect on physical well-being. It is suggested that adequate water intake and muscular exercise may prove effective in combating this tropical alkalosis. Disturbances of endocrine function have an important effect on energy metabolism. Sundstroem found that the basal metabolism varied between 25.5 and 36.1 calories, with an average of 81. Variations in the dry- and wet-bulb temperatures may affect the level of basal metabolism in certain individuals. Radsma concludes that the basal metabolism in Europeans is reduced, or is, at least, lower than the standard values which obtain in Europe and America.

Perspiration.—Adaptation to high temperatures involves an increased capacity to produce sweat, a greater sensibility of the temperature regulatory apparatus, and, probably, a power to limit salt loss. In failure, such as that due to excessive salt loss, or to a steadily rising temperature, the sweat glands may be at fault. Anyone who is exposed to high temperatures should take warning if a degree of exhaustion increases with each day of work, and if his degree of recovery decreases with each night of rest (Dill).

Sweat varies in composition, depending upon its rate of production. In very hot weather, salt depletion is high, not only because of the large volume of sweat produced, but because this sweat is unusually high in salt content. While the sweat glands excrete lactic acid, it is believed that this is not wholly dependent upon muscular exercise.

Thirst.—Thirst does not necessarily depend on a dry mouth, nor does it depend on the volume of blood plasma, or of the extracellular phase of other tissues. It depends upon the diminished water content, and possibly upon increased osmotic pressure, of body cells. While thirst may be somewhat alleviated by rinsing the mouth, it can be satisfied only when water has been delivered by the blood-stream to the tissue cells demanding it (Dill).

PATHOLOGICAL EFFECTS OF TROPICAL CLIMATE

The tropical light produces effects in the skin, which may be acute or chronic. They range from a slight sunburn to a severe erythema, accompanied by blisters and œdema, so that a reaction may set in, accompanied by œdema and septic absorption. Sometimes this may be so severe as to produce delirium, or even coma. Chronic skin irritation is shown by pigmentation and by vasomotor changes ; that this is a process of natural selection is demonstrated by the skin pigmentation of most native races, so that the nearer the equator, the darker the skin, whilst that of a European long resident in the tropics tends to darken. When slight pigmentation is established, probably as the result of increased blood supply, hair and nails grow more rapidly. Freckles—small brown pigmented macules—are specially apt to occur in sandy, red-haired, or fair children brought up in a tropical climate, and are often very disfiguring. Chronic solar dermatitis, or sailor's skin, especially at the back of the neck, is characterized by atrophy, wrinkling, pigmentation, white atrophic patches, telangiectases and warty growths (solar keratoses), some of which, especially when situated on the dorsum of the hands, eventually become the seat of basal (rodent ulcer type) or squamous-celled neoplasms.

Summer eruption is a polymorphic eruption of erythema papules, vesicles, weeping areas, crusts, pigmented macules and small depressed scars, which occurs in exposed parts, especially among children.

Urticaria is occasionally produced by the actinic rays. *Xeroderma* *pigmentosum* (Kaposi's disease) is a congenital condition of light-sensitiveness, such as is produced by X-rays on a normal skin. This manifests itself by pigmentation, telangiectasis, keratoses, and finally epithelioma, and is produced by the ultra-violet region of the spectrum. It is said to be more frequent in the tropics than elsewhere. *The effect of tropical sunlight on the eyes* is well known to produce glare conjunctivitis, necessitating smoked or tinted spectacles. Pterygium, or a triangular fibrous growth extending over the conjunctiva to the pupillary margin with its base towards one or other canthus, is common in tropical residents, and is considered to be a natural reaction to intense sunlight.

The congestive disorders, affecting especially the liver and bowels, are probably due more to sudden changes of temperature. The concentration of the urine predisposes to gravel and probably accounts for the frequency of renal and vesical calculi in tropical residents, especially in hot dry climates, such as that of the plains of India and the arid districts of the Sudan and Northern Nigeria. People living in hot, dry climates with an inadequate water supply (conditions which obtained for the troops in the western desert of Egypt) may suffer from backache or even renal colic, probably due to deposition of salts in the renal pelvis or ureter. It is evident that, where fluid loss is so great, exceptional intake of fluid becomes necessary.

CHAPTER II

LIFE IN THE TROPICS—(*Continued*)

CLOTHING AND GENERAL HYGIENE

TROPICAL clothing must protect the person from solar rays while interfering as little as possible with evaporation of moisture from the body. The clothes should be light and loose, whilst the material which comes next to the skin should be non-absorbent and such as can be frequently washed.

The *sun helmet* (or topee) should be white or khaki and have a dark or green lining. It should not exceed 15 oz. in weight, and the brim, sloping downwards, should project horizontally from the head for at least 5 inches. A posterior projection is useful, and some recommend a flap of aluminium foil. The helmet is known as a solah topee, and is made of pith. At higher altitudes the double Terai hat may be worn. To prevent glare, and to mitigate the effect of light —as some believe that the ill-effects of the solar rays are exercised through the eyes—smoked or tinted glasses should be worn.

Clothing should above all be loose, especially around the neck and chest. The fabrics usually worn are white or light-coloured, and cotton is best. A light flannel shirt is popular. Whenever washable trousers or shorts are not used, light cotton or calico drawers should be worn for the sake of cleanliness and to prevent irritation. A backless waistcoat should be worn in the evenings. Where a coat or tunic is not worn, a spinal pad of dark material is very useful, and a strip of cotton sewn inside the shirt answers the purpose very well. Experimental work in the Philippines has shown that white or khaki are the best colours for external clothing in their power of reflecting heat. Khaki is preferable for thin clothing. White drill is stiff and not well ventilated; tussore silk is better but expensive. Most experienced travellers agree that the lighter the clothing, the better. Shorts are universally worn by men and, once the skin of the knees has become used to the sun, have many advantages, the chief disadvantage being that they expose an extra skin area to mosquito bites. This, however, can be avoided by flaps which can be turned down under the puttee or legging. The provision of slits under the armpits of shirts and tunics is advisable.

Boots call for careful selection and should be half a size larger than those worn in temperate climates, as the feet swell readily in the heat.

Women's clothing in the tropics.—As far as possible women's clothing should be made of fine, soft cambric. It should consist of vest and knickers, which may have to be changed two or three times daily to prevent prickly heat. A loosely-woven cotton gauze, or a mixture of cotton with silk or wool, is best. Stockings, if worn, should be of cashmere, but bare legs are better. A white umbrella, or parasol, lined with green, is almost a necessity.

Children's clothing in the tropics.—Children's garments should be soft, light and loose. In very hot weather cotton gauze is best for underclothing, as the sensitive skin is very liable to prickly heat.

Exercise.—Regulated daily exercise in the open air is necessary for the preservation of health in most tropical countries. It aids the body to get rid of waste material by inducing increased respiration, and is a stimulus to digestion and defæcation. It is customary to take exercise in the early morning and late afternoon. It is a great mistake to overdo hard games such as tennis or squash in a tropical climate to the point of fatigue. This is more likely to be a mistake of newcomers.

Horseback riding is the ideal exercise for the tropics on the adage that the "best thing for the inside of a man is the outside of a horse." A warm bath or a rub down should always be taken on return from exercise.

Sleep and rest.—A sufficiency of unbroken sleep is essential as a protection against the ill-effects of the tropical climate, but unfortunately it is not always easy to obtain. In the hot stuffy nights of the Indian summer, and during the dust-storms of Central Africa, sleep becomes almost impossible, especially when it is necessary to use a mosquito-net which impedes the circulation of the already stifling air. Therefore it is better to sleep in a mosquito-proof room, which permits electric fans. The ideal solution is an air-conditioned bedroom.

In most very hot countries, the daily siesta is customary, and is usually taken after lunch. An hour's rest after the mid-day meal is recommended, especially for European women and children.

Food.—It is scarcely possible to lay down general principles, since individuals and races differ so greatly in their conception of an adequate dietary. There is little doubt that the normal digestive capacity is less in the tropics than in temperate countries. Large quantities of food are not well tolerated, though possibly this may to a certain extent be attributable to monotony. The diet should consist of foods which produce a minimum of heat. Of the true essential constituents, fats and oils have the highest caloric value, hence the almost instinctive aversion of Europeans to greasy and fatty foods in a hot climate. There is usually, also, a distaste for animal food, a fact which, to a certain extent is explained by the poor quality of meat obtainable and the lack of variety in cooking, but it is true that excessive meat-eating is harmful, probably on account of incomplete digestion, unless the body is being actively exercised. This is true for most tropical countries which have a cool season, such as the Sudan or Iraq. Meat can safely be eaten in the cold weather.

Generally speaking, the indigenous products of tropical countries are more suitable for food than any which can be imported. Sugar is a very valuable constituent of the diet in the tropics, especially for Europeans on the march, or on *safari*. Preserved dates and figs therefore have acquired a reputation among travellers, and it is wonderful how sustaining they prove, provided that the requisite quantity of liquid can be procured at the same time.

Breast-fed infants thrive as a rule, and it is said that the quality of the milk of European mothers is usually not impared by tropical conditions. Most women, however, cannot stand the strain of nursing their babies for any length of time. In Panama it has been found that the average milk of the coloured woman foster-mother is richer than that of the European, and often upsets the digestion of the child, and in most parts of the tropics babies must be artificially fed. Cows' milk being very rarely obtainable, it is necessary to use prepared foods, such as Mellin's, or condensed milk. Banana flour is an excellent food for infants.

Beverages.—An ample supply of water is vitally necessary, and the amount varies according to the climate. During the hot weather in the Deccan in India, where the percentage of moisture is very low, it was found by Hunt that Europeans who lived in tents and took a good deal of exercise required no less than three gallons of water per head per day. This was also recognized during the 1914-1918 war, in Iraq, where it was laid down that even a greater quantity than this might be needed under the conditions that prevailed. Even with this supply the excretion of urine was by no means excessive. As much as 1·32 gallons is required to neutralize the heat produced by metabolism, quite apart from the heat added to the body by radiation and conduction. This holds for dry climates, with a high dry-bulb temperature, but in still, moist atmospheres, where evaporation is at a minimum, imbibing large quantities of fluid merely increases the discomfort.

Alcohol.—Widely differing opinions are expressed about alcohol. By some —and it may be said the great majority—it is deemed a necessity and consequently beneficial, whereas by others, except for the old and infirm, it is regarded as a luxury and superfluous. Be that as it may, a moderate amount of stimulant, reserved as a " sun-downer," probably does no harm, reviving the flagging energy and lending some colour to an otherwise monotonous day. It is probable that the average healthy adult male can deal satisfactorily with 1½ oz. of alcohol daily. Alcohol taken with the evening meal promotes good fellowship, stimulates the appetite and aids digestion, but the inevitable whisky and soda between meals is to be discouraged.

Aërated drinks are universal, and are useful in aiding digestion. The " Frigidaire," by providing cooling drinks, which are beneficial in relatively small quantities, has done a great deal towards the promotion of comfort and health in tropical countries.

PRINCIPLES FOR INCREASING BODILY COMFORT IN THE TROPICS

In order to maintain reasonable health in the tropics, and also to preserve working efficiency, it is necessary to improve the measures for promoting bodily comfort by every practical method. Human comfort in hot climates depends upon four factors: (1) the dry-bulb temperature, (2) relative and absolute humidity, (3) air movement, and (4) radiation to and from the surroundings.

When considering this problem it is essential to remember that the average individual is continuously producing 400 British thermal units of heat energy per hour within his body, due to chemical changes associated with circulation, respiration and glandular activity, so that it has been estimated that the resting human body produces, every hour, enough heat to boil a quart of water. It has been shown by direct measurement of the heat loss from the human body of normally clothed individuals sitting in an ordinary room in still air, at a temperature of 59° F. and 50 per cent. relative humidity, that the body loses heat to its environment in the following proportions: 45 per cent. by radiation; 31 per cent. by convection and conduction to the air; and 24 per cent. by evaporation of the moisture given out from the lungs and skin.

Although the mechanism for regulating the temperature of the body may increase the heat loss by sweating, if that heat loss is limited by the environment, considerable discomfort is produced. If the temperature of the walls of a room is 79° F. (in place of 59° F. mentioned), the loss by radiation from the body is already halved. Radiation is increased by artificial methods for promoting currents of air, e.g., by electric fans, and the temperature of the air may be reduced by air-conditioning. These, however, and especially the latter, are expensive measures, only to be undertaken in the larger and well-established centres. Air-conditioning in workrooms and bedrooms is the ideal policy, and is now to be found in most tropical towns, but the expense of maintenance renders it impracticable save for large commercial undertakings.

With the idea of counteracting the radiant heat from the sun and sun-heated surfaces, Crowden has investigated the physical properties of low emissivity and high reflectivity for radiant heat possessed by bright metallic materials, such as aluminium foil. It has been shown by laboratory tests that, by providing sun-helmets with an inside lining of bright metallic foil, the heat radiated to the head is much reduced.

It has been found, too, that the insertion of a layer of aluminium foil in the walls of sheds and lightly-constructed buildings is highly effective. The provision of a one-inch air space and its replacement by reinforced aluminium foil adherent to thick kraft paper, affords insulation approximately equivalent to thirteen inches of brick. Crumpling the aluminium foil, so as to make it occupy all the air space, appears to enhance the effect.

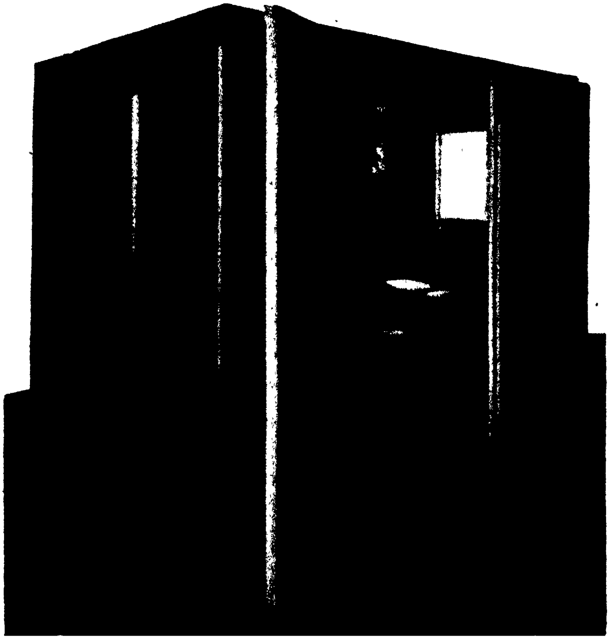


Fig. 1.—Portable air-conditioned cubicle. (*Newcon Industries, Ltd.*)

Preparations of aluminium and aluminium paint can be applied to the inside lining of tents and marquees, and this is a practical measure which is receiving considerable attention for reducing the inside heat produced by radiation. Asbestos paper and cork lining, one inch thick, are also efficient, though expensive, insulating materials.

Acting on these principles, Crowden and Angus have devised a form of portable air-conditioned cubicle. It consists of twenty-one panels, which clip together to make a small room, 10 ft. × 6 ft. × 7 ft. high. The walls are insulated by reinforced aluminium foil in the air space, which prevents the penetration of heat from outside and lessens the load on the small air-conditioning unit serving the cubicle. A power consumption of less than 800 watts has been found adequate for air-conditioning the cubicle under extreme conditions of tropical heat and humidity. It is possible to maintain a temperature of 80.5° F. dry-bulb, 71° F. wet-bulb, 67° F. dew-point, and 65 per cent. relative humidity, with an outside climate of 95° F. dry-bulb, 90° F. wet-bulb, and 88° F. dew-point temperature, with a relative humidity of 82 per cent. The use of such cubicles in tropical bungalows, offices, factories, hospital wards, ambulance room and mines should go far to eliminate the trials of a tropical climate and maintain normal health (Fig. 1).

NUTRITION IN THE TROPICS

Nutrition is of fundamental importance, and the practical application of its main principles to tropical native races has only comparatively recently attracted the attention which it deserves. Even yet, however, the wider implications of the problem are little understood. The whole subject is another illustration of the parable of the soil and the seed. Defective nutrition arising from unbalanced and unsuitable dietaries is now held responsible for many of the ills of mankind, and said to predispose, indirectly, to parasitic infection. Within the space available it is only possible to give an outline of the principles involved.

The constituents of food are proteins, fats, carbohydrates, minerals, vitamins and water. The functions of these substances are so interconnected that those of any one group must be considered in reference to the others, for, although proteins are necessary for building up the body, they can also be drawn upon for the production of heat and work. Again, although the greater amount of carbohydrates and fats is used for this purpose, yet some are also necessary for building up proteins of body cells. The vitamins act as accessory food factors, and are concerned in metabolic processes (*see* p. 394).

Carbohydrates.—The carbohydrates include sugars and starches; they constitute the cheapest source of energy and make up the great bulk of the food of man in most parts of the world. They are divided into monosaccharides and polysaccharides.

Monosaccharides are easily soluble, and diffuse through the alimentary tract, without being acted upon by the digestive enzymes. The three commonest are glucose, fructose and galactose, and, when consumed in larger quantities than are required for the immediate purposes of the body, they are built up into the polysaccharide *glycogen*, which is stored in the liver and reconverted into glucose when required for the maintenance of the normal amount in the blood.

Glucose (dextrose, grape sugar) is abundant in many fruits and vegetables and is also the product of the action of digestive enzymes on all starches.

Galactose is formed, together with glucose, when the digestive enzymes act upon the disaccharide lactose (milk sugar).

Disaccharides are converted into monosaccharides during digestion. Three of them, viz., saccharose, lactose and maltose, are important constituents of food. *Saccharose* is *cane* or *beet* sugar. Pineapples and carrots are particularly rich in it. *Lactose* constitutes 4-5 per cent. of cows' milk and 6-7 per cent. of human milk. *Maltose* occurs in germinating cereals, malt and malt products.

Polysaccharides.—Most of these are insoluble in water. Those available for food are broken up by digestive enzymes into glucose. *Starch* is stored up in plants, especially in seeds and tubers, for requirements of energy and growth.

The action of digestion is to break up the molecules of starch and convert them into soluble *dextrin*. *Glycogen* occurs in all parts of the body, especially in the liver; there are considerable quantities in the muscles and it is rapidly used up during active muscular exercise. *Cellulose* is resistant to the action of digestive enzymes, and gives bulk to the food and appears unchanged in the fæces.

Fats.—*Fats and lipoids* are substances which are soluble in ether, chloroform or benzene, but insoluble in water. Examples of edible oils are olive and coconut oil.

The fats are compounds of glycerol and fatty acids. When fat is treated with a strong alkali, the glycerol is freed, and the alkali combines with the fatty acid to form a soap.

Fatty acids lend consistency to fats. The better known are butyric, caprylic, capric, lauric, myristic, palmitic and stearic acids. The last three are solid under ordinary temperature conditions of the tropics.

The other series of fatty acids have general formulæ in which the number of hydrogen atoms is less than double the number of carbon atoms. They are known as *unsaturated fatty acids* and can take up iodine (or other halogens). Soft fats, or oils, which are rich in unsaturated fatty acids, can be hardened to a desired consistency by hydrogenation.

The fats are composed of the same three elements as carbohydrates, but are superior to them as a supply of energy and for storage. Fats can be synthesized from carbohydrates in the animal body.

Lipoids are not allied to fats in chemical constitution. They are present in the tissues of animals and plants, and are necessary for many vital functions; but the relationship of those taken with the food to those in the body cells is unknown. The *sterols* occur widely in living matter, and when ergosterol is irradiated with ultraviolet light, *calciferol* is produced, which has the physiological properties of vitamin D (*see* p. 410).

Proteins.—The proteins are the chief constituents of all the cells of the body, and form the greater part of all the organs and muscles. All contain the five elements, carbon, nitrogen, hydrogen, oxygen and sulphur.

On hydrolysis, or by the processes of digestion, substances of progressively smaller molecular weights are produced—proteoses first, then peptones, and finally amino-acids, of which twenty-one are known. The amino-acids constitute the nuclei around which the proteins are built, and the different permutations provide an almost infinite number of proteins.

The amino-acids are all compounds of NH_2 groups, with various organic acids. Examples are: glycin, alanin, leucin, aspartic acid, arginine, histidine, and trytophane. Some proteins are rich in amino-acids, poor in others, and there are some proteins, such as *zein* of maize and gelatin, which do not contain any of the important amino-acids. There is a great deal of evidence to show that the nutritive value of proteins is dependent upon the kind and proportion of these acids. Thus, if young rats are fed on zein, which contains no tryptophane, they fail to grow, but recover when this substance is added.

Amino-acids essential in the food are lysine, tryptophane, histidine, cystin, methionine, phenylalanin, leucin, isoleucin, valin and theonine.

Cystin and methionine both contain sulphur and are particularly required for the growth and maintenance of the skin, which is rich in sulphur. There are some, such as prolin and arginine which, capable of synthesis in the body, may not be necessary in the diet of adults, yet cannot be formed fast enough for the needs of normal growth, and hence are necessary for the diet of children.

Proteins have been classified into three groups in relation to their nutritive value:—

(1) "Complete": when one of these is the only protein in the diet, and in sufficient quantity, it can maintain life and support normal growth. Casein and lactalbumin, ovalbumin, glycinin of the soya bean, and gluletin of maize, are examples.

(2) "Partially incomplete": these can maintain life, but cannot support normal growth. Gliadin of wheat, hordein of barley and prolamin of rye are examples.

(3) "Incomplete": these are incapable of maintaining life or supporting growth. Zein of maize and gelatin are examples.

The body requires a steady supply of protein for the repair of tissues, such as the hormones. The muscles, when at work, utilize carbohydrates and do not break down their proteins to more than a very small extent.

It has been determined that about 3 grm. of nitrogen represents the endogenous expenditure of a man weighing about 154 lb., corresponding to about 18.75 grm. of protein for the maintenance of the body.

The term *digestive utilization* implies that the proteins of various foodstuffs are not equally digested or absorbed. The digestive utilization of meat, fish and milk is much higher than that of vegetable products.

Biological value is a term used to express numerically the ability of proteins to satisfy the nitrogenous needs of the body. The numerical figures give some indication of their comparative values. Thus, of animal products, beef muscle is reckoned at 98, and shell-fish at 72, whilst maize flour is standardized at 60. The quality of a protein for body maintenance of the adult can be expressed in numerical terms, but the relative requirements of children and adolescents are continually changing; thus a protein of poor value in the early stages of life may become more valuable in later years when growth requirements are declining and maintenance needs increasing.

For growth it is shown that the proteins of animal origin have a marked superiority over those of vegetable origin, while milk holds pride of place for growth-promoting properties.

The protein requirements of pregnancy can be easily estimated. The fœtus and adnexa contain an average of 100 grm. of nitrogen, which may be represented as 625 grm. of protein. This amount is built up in 270 days of pregnancy, and thus the mean production is 2·3 grm. When this is added to the maintenance requirements the total is 17·5 + 2·3 = 19·8 grm., but the protein needs are not evenly spread over the whole period of pregnancy, less being required during the earlier than during the later months. A woman during pregnancy, however, is able to store proteins as a reserve against the demands made upon her during lactation.

There are some common *diseases of the tropics* which greatly increase the metabolic rate, and, although carbohydrates and fats are mainly affected, the increased output of nitrogen and the wasting of muscles indicate increased breakdown of the proteins. Malaria is one of these, and so are the prolonged fevers of the typhus, typhoid and undulant groups. An adequate diet should contain proteins from a variety of foodstuffs, so that all necessary amino-acids will be present in adequate amounts.

Animal products supplement cereals better than vegetable products for growth.

Minerals.—Many minerals are present in the body; for instance, calcium, phosphorus, potassium, sulphur, sodium, chlorine, magnesium, iron, manganese and iodine, with traces of copper, zinc, fluorine, silicon and aluminium. All these elements in the human body are necessary for growth and health, as they enter into the constitution of all the tissues, and are present in large amounts bones and teeth, and as soluble salts in all the fluids of the body, where they maintain neutrality, osmotic pressure and solvent powers, supply electrolytes for the action of muscles and nerves, and produce acidity or alkalinity in the digestive and other secretions.

A healthy, active man excretes daily from 20–30 grm. of mineral salts as chlorides, sulphates and phosphates of sodium, potassium and calcium, and small amounts of ammonium salts derived from protein metabolism.

Salt taken with food supplies the necessary amount of sodium chloride. The quantity of different minerals in foodstuffs of vegetable origin directly depends on the soil on which they are cultivated. Some minerals are present in all possible human diets in quantities considerably greater than the needs of the body. Sodium chloride, for instance, is present in quantities in most human diets, but there are tribes in Central Africa to whom common salt is not easily accessible, so that the custom of using mineral earth or plant ash has developed. The term *pica*, applied to certain manifestations of a depraved appetite, such as earth-eating or bone chewing, is frequently observed in native people as a sign of mineral deficiency.

Manganese has been shown to be essential for growth and health, and is present in vegetable in far greater quantity than in animal tissue.

By far the greater proportion of *sulphur* in the tissues is derived from the proteins of the food.

Calcium, phosphorus, iron and *iodine* have been shown in various parts of the world to be deficient in human diets. The greater proportion of the calcium and phosphorus in the body is found in the bones and teeth and these elements are liberally supplied in the milk of all species. When stunted growth and decay of teeth are prevalent the adequacy of calcium and phosphorus in the diet has to be considered.

Iron is present in the body in small amounts, but is of vital importance since it is an essential element in the formation of the hæmoglobin of the blood, which contains thirty times more iron than does the rest of the body. When blood-corpuscles become effete and are broken up, the greater part of the iron is retained in the body and is used again for the formation of hæmoglobin. Microcytic hypochromic anæmia, which is very common in the tropics, especially in ancylostomiasis, is due to iron deficiency. During pregnancy there is a withdrawal of iron from the mother's body to supply the fœtus.

Iodine is necessary for the formation of thyroxin, the hormone of the thyroid gland which regulates metabolism. There is about 15 mgm. of iodine in the thyroid gland of an adult man, but only 10 mgm. in the rest of his body. Iodine is present in sea-water, and products of the sea, such as fish, seaweed and salt, contain appreciable quantities.

THE ENERGY VALUE OF FOOD

The energy value of food is supplied by carbohydrates, fats and proteins, and is expressed in terms of heat-units or *calories*. A *calorie* is the amount of heat required to raise the temperature of one kilogramme of distilled water from 15° to 16° Centigrade.

The apparatus utilized for the purpose of determining calorie values is *Atwater's bomb calorimeter*. The heat combustion of organic substances depends upon their chemical composition. The total energy requirements of the body are conveniently expressed in calories per day, either for the whole body, or per kilogramme of body weight. The quantities of food in terms of calories which are necessary to support normal metabolic processes may be studied from the point of view of requirements for *basal metabolism*, requirements for *general maintenance*, and requirements for *work*. The recommendations of the League of Nations on energy requirements are as follows:

For an adult man or woman living in a temperate climate, an allowance of

2,400 calories is considered adequate, but the following supplements for muscular activity are to be added : for light work 75 calories per hour of work, and for very hard work 300 per hour of work.

The average size of most tropical races depends largely on the status in life but, taking populations as a whole, the mean stature is smaller than for populations living in temperate climates. The mean weights of men and women of most tropical races is about 115 lb. for the former and 100 lb. for the latter. It therefore follows that the maintenance allowance of 2,400 calories is too high, and 2,100 is sufficient, whilst the energy value of the food of the average labourer in the tropics may be placed at 2,600-2,700 calories *per diem.*

The balancing of diets for poorer classes of natives, so that the proteins shall be adequate in quality and quantity, obviously presents many difficulties. It is generally accepted that the daily protein allowance should be 100 grm., with the proviso that it shall include 37 grm. of protein of animal origin ; but the figures accepted for temperate regions are too high for the tropics, and those for India are considerably lower. There the requirements for men are 65 grm. ; for women 55 ; for growing boys 80, and adolescent girls 70 grm. *per diem.*

The weight of fat in the diet should be about the same as that of proteins, and should not fall below 50 grm. daily. Butter and ghee are preferable to vegetable oils. The main function of the carbohydrates is to supply calories in all cases where additional energy is required for work. This should be supplied by foodstuffs rich in carbohydrates, such as rice, bread and other cereal foods.

The calories of a diet consisting mainly of rice, dhal, coconut and green vegetables, such as is commonly in use throughout India and Southern Asia, are sufficient for the average man ; and the proteins, although not of a high biological value, are just enough for an adult. But such a dietary is usually deficient in calcium, while the supply of adequate protein of high biological value is not sufficient for growth and maternity ; the addition of fish increases the supply of calcium as well as of protein.

The effect of dietary upon the physique and health of tropical natives has been specially studied by Orr and Gilks (1931). A survey of two tribes in East Africa, the Masai and the Kikuyu, was undertaken. The former subsist mainly on milk, meat and raw blood, and on an average are 5 in. taller, 23 lb. heavier and 50 per cent. stronger than the latter, who live mainly on cereals, roots and fruit. Marked differences were found in the incidence of disease in the two tribes. Bony deformities, dental caries, anæmia, pulmonary conditions and tropical ulcer are very much more prevalent in the Kikuyu, whilst intestinal stasis and rheumatoid arthritis are more common amongst the Masai.

Tables of the nutritional value of the main foodstuffs of Central African natives have been prepared by the Imperial Bureau of Animal Nutrition. It is generally agreed that the native must have better food if he has to have better health. Admittedly it is difficult to assess the effects of different diets upon particular native peoples, since the metabolism of African natives is little understood. There is no doubt that improved nutrition calculated upon a scientific basis should confer enormous benefits upon the British Colonial Empire, and indeed upon all natives of the tropics, not only in eradicating deficiency diseases, but also in reducing the very high infantile mortality which is found almost everywhere. This question formed the subject of a searching enquiry by a Government Committee on Nutrition in the Colonial Empire (February 1939).

One of the most striking outcomes of this enquiry has been to show the almost complete absence from tropical diets of milk, or indeed of animal products, in all native communities, with the possible exception of the West Indies. striking fact is the extent to which native peoples depend on a *single* *crop* for their main supply of food. Indeed, it may be said that a low standard of living is almost universal. With such a diverse range of climates, environment, peoples, customs, prejudices and beliefs, it becomes almost impossible to generalize, so that the kind of diet which will give the best results must always be worked out on the spot for each territory. Ignorance, tradition and prejudice still remain the most important factors in this problem.

In working out the energy requirements of the body in native communities, recent work has shown that the formula should be computed upon the surface area of the body. The formula commonly employed is that of Du Bois, which is as follows :

Surface area in sq. centimetres = wt. in kilos. × 0·45 + height × 0·725 + 71·84 (a constant).

The biological value of food may vary very considerably, and it is common knowledge that the soil in which a foodstuff is grown, the method of manuring, the time and method of harvesting, the methods of storing, marketing, processing and cooking, all have a very marked effect upon the value of the food when consumed, so that proper allowance has to be made for all these factors. Moreover, many factors react upon the state of nutrition by affecting the metabolic processes in the body, such as the hygienic surroundings, high humidity, traumatic states and pathological processes which interfere with powers of absorption. There is also the possible action of *toxic substances* in the food. In the examination of native dietaries, it should be remembered that untoward results may be due to cyanides, fluorides, and even to parasitic growths and contamination from storage.

Native diets, with a few exceptions, are predominantly vegetarian, and relatively small quantities of animal products are consumed. Maize, rice, millets, guinea-corn, groundnuts, beans, peas, cassava, yams, coco-yams, tannias, sweet potatoes, plantains, bananas, gourds, coconuts and other palm products and numerous leafy vegetables are the main raw material. The outstanding feature of the diet, judged by European standards, is that an unusually high proportion of the energy value is derived from carbohydrates. This is at the expense of fat, which is usually very low, except in areas where coconuts (as in Malaya and the Pacific) or other palm products (in South Nigeria and West Africa) are largely consumed. Since it is necessary to consume two and a quarter times as much carbohydrate, by weight, to obtain the same amount of energy as from one unit of fat, it follows that the diets are also bulky, relative to their nutritive value.

This does not by any means imply that most native races eat *too much food* ; much more often they eat a great deal less than they ought to do. Although, under the present circumstances, there is no actual famine, yet there is frequently a shortage owing to bad harvests, plague, locusts and economic stringencies. If the diets are unduly bulky, the bulk is made up of foodstuffs unsuitable for nutrition.

The diet of pastoral tribes in Kenya and Tanganyika consists chiefly of meat, blood and milk, and in North Nigeria also animal products are easily obtainable, whilst for the nomad Somali camel's milk is the staple article, but these are quite exceptional cases. Wherever meat is available it is poor in quality, deficient in fat, and far too expensive for poorer classes. Fish is most used by those to whom it is easily available on the seaboards, river or lakeside, and is commonly eaten fresh or dried but, except in the Pacific Islands, it does not constitute the main article of diet. There is a general deficiency of fats which, when procurable, are drawn from vegetable sources. This is deleterious, as fats are vehicles for vitamins A and D. Added to this, there is a deficiency in the consumption of leafy vegetables and fruits, and therefore of vitamin C.

Beriberi (p. 414), a deficiency of vitamin B_1, occurs most frequently in countries where rice is the staple food, as in China and Malaya. In the Straits Settlements it still causes, on an average, 900 deaths a year.

Probably there are a great many borderline cases where comparative malnutrition leads to a general lowering of health without eliciting the recognized symptoms of the classical disease.

Special crops which should be encouraged from the point of view of nutrition are now receiving attention, and amongst these the soya bean (*Glycine hispida*) and the groundnut (*Arachis hypogœa*) are worth mention, for they both contain protein of good biological value and a high proportion of fat. The groundnut contains between 20 and 30 per cent. of good protein and as much as 40 to 50 per cent. of fat and is rich in B_1. The soya bean is particularly rich in calcium, and in its mineral, fat and protein content compares favourably with most vegetables. Unfortunately, it is not an easy crop to establish. There are other legumes which are of special value as foodstuffs—the pigeon pea (*Cajanus cajan*), cow pea (*Vigna unguiculata*), black and green grams (*Phaseolus mungo and P. aureus*), tepary bean (*P. acutifolius*), Lima bean (*P. lunatus*), dolichos bean (*Dolichos lablab*), and haricot bean (*P. vulgaris*).

A number of other vegetables are of nutritive value, including yams and potatoes. The red and yellow sweet potatoes are good sources of the precursors of vitamins A and C. For oils and fats, of which there is generally a deficiency, several palms are found in West Africa, especially for the red palm oil obtained from the fleshy pericarp of the fruit of *Elæis guinensis*, which, as far as vitamin A is concerned, is equal to good cod-liver oil. The kernels also contain a special oil known as "palm kernel oil," which is also used in food and for many other purposes. The cultivation of these oil palms is a special industry in West Africa and they have now been introduced to Sumatra and the West Indies. The importation of this palm is to be encouraged wherever the soil and climate are suitable. "Shea butter" is obtained from the nuts of the wild shea tree (*Butyrospermum parkii*) and is also a considerable source of fat.

In surveys of native populations the presence of Bitot's spots (*see* p. 398), xerosis of the cornea and conjunctiva, with phrynoderma (*follicular hyperkeratosis*), lichen pilare, and often glossitis and angular stomatitis, afford a simple method of assessing the nutritional state, especially in large groups of children.

The principal diets of native races may be summarized as follows:—

Africa (East Africa, Somaliland, Uganda, Tanganyika, Kenya, Nyasaland) :— The natural food of the nomad Somali is milk and meat with additions of ghee, rice and dates. This diet lacks variety, and the imbalance is due to fat excess, resulting from milk and ghee. There is a striking absence of deficiency diseases. In Kenya different tribes have entirely different dietetic habits. The diet of the Masai consists chiefly of meat, blood and milk, whilst that of the Kikuyu (and indeed most others) is composed of maize, tubers and legumes. In Tanganyika the diet consists of millet, maize, rice, groundnuts, beans, cassava (*Manihot utilissima*), sweet potatoes (*Ipomœa batatas*), bananas, and occasionally fish and meat, mutton, goat's flesh, milk and blood. Tabus and tradition are important factors in dietary shortages, and a tabu on eggs and milk may operate even during a time of shortage. Owing to trypanosomiasis, the people in two-thirds of the territory are prevented from keeping domestic animals. In Uganda the diet is chiefly vegetarian. Plantains form the staple article in parts of the eastern, northern and western provinces ; in the rest of the country grain is the staple, the small millet (eleusine) being the commonest. Again, beans and peas may be the staple. Sweet potatoes, great millet (sorghum), cassava, sesame, pumpkins, gourds and native spinach are secondary foods. Locusts, grasshoppers and white ants are universally eaten as delicacies.

In Nyasaland maize is the staple foodstuff, except in areas where the soil is unsuitable and cassava is relied upon. The staple food, whether maize, cassava or millet, is eaten as a porridge. The amount of milk consumed varies from tribe to tribe, but it is not taken by adults. Eggs are neglected because of tribal tabus. The intake of first-class protein is entirely inadequate. Throughout West Africa the nutritional level is considerably higher than in the Central portion or on the East Coast, and there is a great variety of proteins and fats.

In the Northern portion, on the Gambia, where seasonal crops are grown, the staple article of diet is imported rice, but in the winter months, millet and guinea corn take its place. Secondary foods are yams, coco-yams, cassava, pigeon pea, ragi, okro, pumpkin, tomatoes, citrus and other fruits. On the Gold Coast and Sierra Leone the staple articles of diet in the northern territories are millet, guinea corn, yams, Fra-Fra potatoes, supplemented by maize, groundnuts, tomatoes, onions and shea butter. The shea tree grows especially in Northern Nigeria and the Gold Coast, and has recently been introduced into Uganda and other parts of East Africa. In the southern portions there are in addition plantains, meat and fish. In Nigeria, beans, milk, eggs, meat and green vegetables are procurable, and also a certain amount of honey, and there is abundant shea butter.

In *Malaya, the East Indies and Southern China* the food supply is wide and varied, and is ample in most towns for those who can afford it. Rice is the most important food, and is supplemented with root vegetables, leaves and pulses. Fat supplies in Malaya are obtained from the red unbleached palm oil produced locally, which is a source of vitamin A. On the whole there is deficiency of vitamin B products and protein.

In most parts of China soya bean products supplant milk protein, and the low protein values of blood plasma in the majority of the population may be due to this fact. Therefore relatively slight loss of albumin, as in chronic albuminuria or pleural effusion, suffices to upset the balance and leads to hypoprotinæmia, nutritional œdema and perhaps liability to tuberculous infection. The Chinese do not use dairy products and, in place of butter, eat considerable quantities of peanut and sesame oil in the North, and soya bean oil in the South.

The chemical constitution of the phospholipids of the Chinese differs from that of Europeans. The fatty acids of the blood plasma of normal Chinese are highly unsaturated, indicating the presence of fatty acids of the linoleic series.

India and Ceylon present a special problem on account of the diversity of the population. The Hindoos, for instance, are precluded by their religion from eating meat. The staple articles are rice (most of which is polished), coconut, leafy vegetables, yams, tubers, beans, lentils, peas, dhals and gourds, which are cooked into curries of various types. Curry stuffs consist of chillies, coriander, saffron, garlic, nutmegs and fish ; the latter is the principal animal foodstuff eaten by the poorer classes. Milk is seldom used. The diet in the towns is superior to that in the rural areas. Tea is the principal beverage in Ceylon and in South India ; toddy made from fermented sap of coconut is also widely used, and the toddy yeast is rich in vitamin B. The most serious deficiencies in the diet of the masses are animal protein, calcium, and vitamins A and B. To improve the calcium content, greater use of small fish (the bones of which contain the necessary calcium) and leafy vegetables is advocated.

Nicholls in Ceylon has shown the food value of the egg-plant (*Solanum melogena*) and has analysed the substances in the edible portion, as reported from five countries. The highest protein content is from Malaya (2·2 per cent.), whilst the lowest is from Java (1 per cent.), and the calcium and iron contents also vary proportionately. Orr has stated that in no part of the world is the problem of nutrition more serious than in India, where there are only two rice bowls for three mouths. The fundamental difficulty is shortage of food, and the problem is one of agricultural re-orientation and development to provide more food, especially milk and other protective foods for human consumption.

West Indies and South America.—The average diet of the working classes in Barbados, Jamaica and other West Indian islands consists chiefly of rice, flour and other cereals, sweet potatoes, yams, onions, salt pork or beef, salt fish, sugar and tea. Milk consumption is low, and in the majority of cases condensed milk is used. There is a shortage of milk, eggs and fresh vegetables. The weekly wage of parents does not usually suffice to feed the whole family, so that the children, after the middle of the week, receive no regular meals. In Jamaica, cows' milk is rarely taken, even when available. Fat, of which the chief source is coconut oil, is deficient in most diets. Vegetables, such as pumpkins, onions and tomatoes are not extensively used. Special stress is laid on the shortage of protein in the island products. A high percentage of the population suffers from varying degrees of subnormal nutrition.

In *British Guiana*, *Venezuela*, *Brazil* and the tropical parts of South America, rice is grown over wide areas and is the staple article of food for more than a quarter of the population ; maize is grown to some extent. Sweet potatoes, tannias, yams, cassava, bananas, plantains and bread fruit are commonly used. Although there is usually a protein deficiency, there cannot be said to be a shortage of fresh meat, and there are many varieties of local fish, whilst eggs and milk are fairly plentiful. The main difficulty about milk is its unsatisfactory quality, due to adulteration and contamination. Fats are generally deficient and are obtained mostly from coconuts and avocado pears.

RICE (*see* p. 416)

Rice forms the staple food of nearly one-half the world's population. It is at present being produced in amounts sufficient to supply one-fifth of the caloric requirements *per capitem per annum.* It is estimated that there are about 200 million acres of land under rice cultivation ; two-thirds of the area is shared equally between China and British India, and about 60 per cent. of the world production is grown in the British Empire. The food intake of the peoples who subsist on it is as much as 80–90 per cent. rice.

The proteins of rice are of a good quality, their biological value for man approximates very closely to that of beef, and the amino-acids compare in amount very favourably with those of other proteins, but the mineral constituents are low and the needs for calcium and phosphorus are not met by either unmilled or polished rice (*see* p. 417).

During storage, serious changes may occur, detrimental to the food value, and in native hands they frequently do. It is possible to feed on rice which has been well milled, as a staple food, without developing signs of beriberi, provided that it is stored so that its vitamin B_1 is not lost.

Rice can be stored without its husk with as good or better results than with the husk on. Rice should not be over-washed before cooking. The widely used process of "parboiling" consists of soaking rough rice in either cold or hot water in cement or metal tanks. After draining off the water, the grains are submitted to steam until the hulls are opened slightly. This soaking may last four days. In the process of parboiling a proportion of the water-soluble vitamin B_1 diffuses throughout the grain, and is therefore conserved whatever the subsequent milling or polishing processes ; nevertheless it is estimated that on a diet of parboiled rice no less than 150 international units of vitamin

B_1 must be supplied daily in other components of the diet (as, for instance, by 6 oz. of dried beans or 3 oz. of groundnuts).

Rice must be cooked in such a way as to retain vitamin B_1.

In the best conditions there is no crop of comparable nutritional value which can approach rice in the amount of food produced in a given area, and in its suitability for man.

NATIVE CUSTOMS AND BELIEFS

In dealing with primitive peoples, whose habits and customs are regulated by long-standing beliefs and traditions, a considerable amount of attention should be directed to this subject, as it undoubtedly plays a dominant part in the public health of the community. This, however, is a stupendous task, requiring a sympathetic understanding which can only be acquired after long residence in the particular area. It is a subject to which in the past medical men have perhaps paid too little attention. Nowhere, however, do these beliefs and customs play so great a part as in Africa, and the student cannot do better than consult Lord Hailey's classical African Survey (1938).

COMMON DISEASES IN THE TROPICS AND THEIR MODIFICATION BY TROPICAL CONDITIONS

The institution of special schools and courses in tropical medicine and the remarkable discoveries which have been made in this branch of science have tended to foster the idea that tropical diseases necessarily predominate in tropical countries. The fact is that most of the ills which afflict mankind occur nearly everywhere, but their incidence and frequency appear to be influenced by local circumstances. Moreover, the clinical picture of a familiar disease may be modified or masked by some superadded parasitic infection. Indeed, a complex pathology in the tropics is the rule rather than the exception. This subject, which has been named " geographical pathology," has received serious attention during recent years and has provided data of considerable importance. While it is manifestly impossible in a book devoted to tropical diseases to go into details, a general survey of universal diseases is useful.

DISEASES OF THE DIGESTIVE SYSTEM

Little is known about variations in gastric secretion in the tropics, save that in ancylostomiasis and other worm infestations the secretion of hydrochloric acid by the oxyntic cells is reduced ; but it is a striking fact that gastric and duodenal ulcers are seldom encountered in native races living on a simple carbohydrate diet. This applies especially to Indians, Javanese and Negroes. As the result of 2,170 autopsies, Kouwenaar in Java concluded that ulcers of the stomach and duodenum are found only in 1 per cent. of Javanese as against 10 per cent. of Chinese, but they are said to be very common in Abyssinians, and this fact is ascribed to dietetic causes (Bergsma). Wanless finds them common in rural districts of western India, due to septic mouths and excessive stimulation by hot curries. Diverticulosis and diverticulitis appear to be very rare or almost unknown.

APPENDICITIS

Inflammation of the appendix is rare, and fulminating cases requiring immediate operation seldom occur in native races, in marked contrast to the frequency of this condition in European residents. In Indians, both Moslems and Hindoos, acute appendicitis is extremely rare and the Editor has seen only two cases in over thirty years.

CARCINOMA OF THE STOMACH AND INTESTINAL TRACT

The rarity of malignant growths in the alimentary tract in native races has been the subject of much speculation. De Langen has laid special stress on the fact that gastric carcinoma is noticeably absent among the Javanese. The same is true in India and, as far as can be ascertained, in Central Africa. The comparatively short life-span of natives, in contrast to that of Europeans, may account for this difference.

CIRRHOSIS OF THE LIVER

All writers on tropical pathology have laid stress on the frequency of liver cirrhosis with ascites among native races, where the influence of alcohol can be discounted. Some of these may be due to syphilitic disease of the liver. Excluding cases caused by parasitic infection there remains a residue, of unknown ætiology, resembling the cirrhosis of Lænnec. Oudendal and other Dutch observers believe that the condition arises from chronic intoxication in a liver deprived of glycogen by undernourishment and starvation.

Wilkinson in South China advances reasons why chronic vitamin B_1 deficiency may be an ætiological factor. Snapper regards this as one of the commonest diseases of China and attributes it to intestinal intoxication in conjunction with deficiency of vitamins of the B complex. It is especially common in association with chronic bacillary dysentery and malnutrition. Megaw in India came to much the same conclusions (*see* p. 474). Hyperprotinæmia is invariable, and there is inversion of the albumin-globulin radio. The serum therefore gives a positive globulin test (*see* p. 168) and differential diagnosis has to be made from tuberculous peritonitis, adherent pericardium and kala-azar. A venous hum is audible between the xiphoid process and umbilicus.

Banti's syndrome with splenomegaly, anæmia, leucopenia and thrombocytopenia, with varying degrees of liver cirrhosis, is also met, especially in China (*see also* Infantile Cirrhosis, p. 551).

DISEASES OF THE GALL-BLADDER

The rarity of cholecystitis in native races is striking. As the Editor has pointed out, there appears to be no direct connection between dysenteric infection and inflammation of the gall-bladder, nor is there any predisposition to cholelithiasis. De Langen and Lichtenstein report that among 150,000 out-patients in Batavia they were only able to make a diagnosis of gall-stones once, and among 422,948 other patients thirty times. Intrahepatic cholesterin stones, however, appear to be not infrequent.

DISEASES OF THE BLOOD

THE TROPICAL ANÆMIAS

Macrocytic Anæmia of Pregnancy.—*Synonym.*—Tropical macrocytic anæmia.

Macrocytic anæmia has for some time past been recognized in India, Malaya, West Africa (Gold Coast, Russell) and other parts of the tropics, in pregnant women. In India it has been differentiated by Wills and others from the pernicious anæmia of pregnancy in temperate climates. The macrocytic anæmia of pregnancy comes on gradually during the second month, but the final breakdown may be sudden. As in pernicious anæmia, many of the clinical features are referable to decrease in the number of red blood-corpuscles. The tongue may be sore, but nerve changes are absent, and the oxyntic cells of the stomach secrete hydrochloric acid. Œdema of the feet and ankles is associated with low blood-pressure and pyrexia. Retinal hæmorrhages are common. This anæmia is essentially due to dietetic deficiencies, aggravated by superadded infections of malaria and ancylostomiasis ; there appears, therefore, to be no essential difference between the macrocytic anæmia of pregnancy, as described by Wills and Mehta in India, and the nutritional macrocytic anæmia which has been made the subject of special studies in Macedonia by Fairley, Bromfield and Kondi. In macrocytic anæmia of pregnancy, many patients survive to term, but collapse during parturition. Premature labour is usual, unless the disease is treated in time, or, as on the Gold Coast, the child dies in the first few weeks of life. Anæmia associated with albuminuria suggests toxæmia of pregnancy. If this condition is recognized in time and treated by blood transfusions and liver therapy, patients may proceed to term, but the children, though not themselves anæmic, are usually feeble. The response of this type of anæmia to liver therapy suggests that it is due to the lack of hæmopoietic principle. It is apt to recur in subsequent pregnancies.

Nutritional macrocytic anæmia.—This form is probably universal wherever the population is living on an unbalanced and deficient protein dietary. Nutritional anæmia is associated frequently with malaria, syphilis, and in India also with ancylostomiasis. Fairley, Bromfield and Kondi now recognize a *macrocytic hæmolytic type*, which is prevalent in Macedonia, and is accompanied by splenomegaly from chronic malaria infection. In this type there is primary nutritional deficiency with a hæmolytic agent—the malaria parasite—superadded. Males as well as females are affected. In addition to the anæmia there is a tendency to leucopenia with a shift to the left and a decrease in the platelet-count.

Trowell (1943) contends that it is better to think of the patient as having nutritional anæmia complicated by an infection of malaria or hookworm.

The anæmia is distinctly macrocytic. The average corpuscular diameter is about 8·6 μ. The red cells are, as in pernicious anæmia, more reduced than the hæmoglobin. There is much anisocytosis, but less poikilocytosis than in pernicious anæmia. Sternal puncture and the hæmocrit tube are necessary for diagnosis. Trowell bases his classification on examination of the bone marrow as well as the blood examination and mean corpuscular hæmoglobin concentration. There is a mixed megaloblastic and normoblastic reaction in the marrow. Most cases show mixed deficiency of extrinsic factor and iron. Where megaloblasts are found in the marrow, liver extracts are needed for treatment.

Treatment.—This anæmia responds quickly to liver or liver extracts. Crude extracts are most effective; larger doses are required than in pernicious anæmia. It is said that anahæmin is not effective.

Differential diagnosis.—In pernicious anæmia there is achlorhydria and a positive van den Bergh reaction, whilst in tropical nutritional anæmia the opposite obtains. Glossitis is said to be much commoner than in pernicious anæmia. Tropical nutritional anæmia has also to be distinguished from the macrocytic anæmia of sprue.

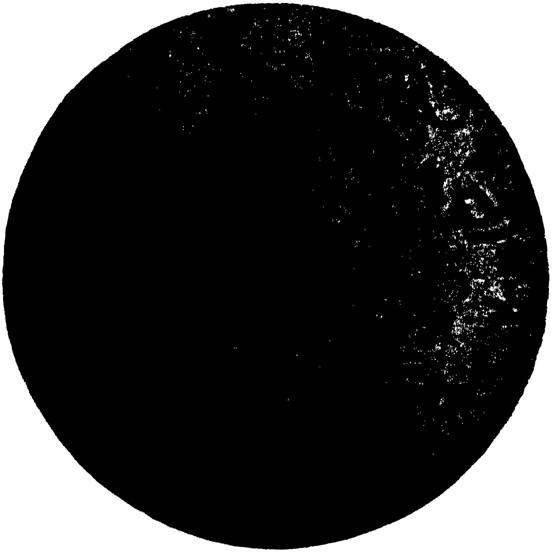


Fig. 2.—Sickle cells. Fresh blood preparation after forty-eight hours. (*Bulletin of the Johns Hopkins Hospital.*)

Sickle-cell anæmia.—Sickle-cell disease is a severe hæmolytic anæmia in which the red cells assume a peculiar sickle shape after withdrawal from the body (Fig. 2). It occurs almost exclusively among
)es, though sometimes found in mulattos. Rosenfeld and Pincus have
d it in Italians, Cooley and Lee in Greeks, Sights and Simon in white
ricans, and Wallace and Killingsworth in Mexicans. It has also
found in wild deer in America. It is characterized by remissions
exacerbations of the anæmia, associated with joint pains and a
ncy to ulceration of the legs. First described by Herrick in 1910, it
ed the basis of a fine study by Huck (1923). Nearly all the cases
been described in the United States. On the whole, it is a rare

disease, and the sickle cell trait is present in 5–7 per cent. of all American negroes, quite irrespective of health.

This disease probably originated in Africa, whence it was imported into the United States; and recently the sickle-cell trait has been found by Evans in 20 per cent. of bloods in the Gambia. Archibald found a case in an Arab from the Sudan (1926), and there are other scattered records from Nigeria and the Gold Coast (Russell and Taylor, 1932). It is a hereditary and familial disease with a Mendelian dominance, and is transmitted equally by male or female. Cooley and Lee have drawn attention to the probable tribal origin and Murray-Lyon to its importance in West African troops. The sickle cell trait is not invariably associated with anæmia.

Sickle-cell anæmia has to be distinguished from ovalocytosis, which is a hereditary familial condition, in which the elliptical shape of the red cells (like that in camel's blood) is transmitted in a Mendelian manner. The young red cells in the bone-marrow have the normal round shape, and assume an oval form when they become mature.

Sickle-cell disease begins in childhood, and males are affected three times as frequently as females. Symptoms may appear even at seventy-eight years of age. The red cells are larger than normal, and show either a normal or decreased fragility. The sickling develops usually only after the blood has been withdrawn. Ordinary stained blood films reveal the sickle shape only in very severe cases. Scriver and Waugh (1930) showed that local moist stasis, produced by a rubber band round the finger, very materially increases the proportion of sickle cells. This is considered to be the most reliable and practical method (Diggs and Peltit, 1940). The wet-blood films should be ringed with vaseline and allowed to stand overnight. Cooley and Lee have shown (1926) that in preparations kept in the incubator the sickle cells disappear, leaving the normal round cells intact.

The latent phase of the disease is much commoner than the active one; in that only a few sickles can be found in perfectly fresh blood, but large endothelial cells may be seen engulfing red corpuscles. Nucleated red cells are always present (Cook and Meyer, 1915). In severe cases the red cells are reduced to 2–3 million, and the leucocytes increased to 15,000 per c.mm. Basophilic stippling of the red cells is common and the blood platelets are not diminished (Mason, 1922).

Pathology.—The bone-marrow is hyperplastic and contains sickle cells. The spleen may be enlarged or may be atrophic and fibrotic. Rich has described characteristic lesions in the spleen: there is a congenital malformation of the sinuses, which permits free escape of blood into the pulp, and this is especially marked round the Malpighian bodies. Osteoporosis of the bones is common. The sickle character can only be recognized in formalin-fixed sections. Graham (1924) has made a minute pathological study of this disease and finds chronic hepatitis and cholelithiasis common.

Symptoms.—Sickle-cell anæmia may remain latent throughout life. On the other hand, there may be an active phase causing severe chronic anæmia of the hæmolytic type, associated with weakness, dyspnœa and a tendency to ulceration of the legs resembling indurated syphilitic ulcers

(Huck), a yellowish discoloration of the scleræ, and jaundice, especially when blood destruction is very great. The liver and spleen are usually enlarged. There may be thrombi in the small vessels of the lungs, giving rise to symptoms of cardiac disease. There is usually a positive indirect van den Bergh reaction.

When the disease is active there may be intermittent paroxysms of fever, associated with severe joint pains which may last two or three weeks. Patients with this anæmia usually do not live beyond middle age, and death takes place from intercurrent infections. Cerebral necrosis, and thrombosis with paresis, have been recorded. The latent disease may be stimulated into activity by any infection.

Blood changes.—Sometimes the blood is macrocytic, and there is a neutrophil leucocytosis of 10,000–30,000. Polychromasia is marked; there is a reticulocytosis of 25 per cent. and normoblasts are common.

If citrated blood is kept under oil for twenty-four hours, and formalin then added, the test for sickle cells becomes more delicate.

Treatment.—The treatment is purely symptomatic. The anæmia may be improved by iron and liver therapy. Blood-transfusion is of distinct value in relieving paroxysms of blood destruction. Splenectomy has been employed with some benefit in selected cases, but the sickling is unaltered by this operation, which renders the patient more susceptible to subsequent subtertian malaria.

Baghdad spring anæmia.—A new form of acute anæmia is reported in Baghdad, appearing only for a few weeks in spring. This anæmia, according to Lederer, runs a very rapid course, and a severe degree is produced within 24 to 36 hours. The mortality is about 10 per cent. It is curable by blood transfusion, liver therapy in massive doses and injection of adrenalin. The disease is confined to boys, for the main part Jews, especially those of a certain constitutional type. It is suggested that the hæmolysis is due to anaphylaxis by contact with flowers (*Verbena hybrida*) and young fruits. The administration of blood has a double effect, counteracting shock as well as stimulating the bone marrow. In mild cases whole blood injections (10–20 c.c. intramuscularly) suffice; but in severe degrees intravenous transfusions are necessary.

Chlorosis.—This has almost disappeared from Europe, but is probably related to the *hypochromic, microcytic dietetic anæmias* (*chlorosis tarda*) of the tropics, which are such a frequent accompaniment of subnutrition and are due to lack of iron intake and absorption. This condition is seen especially in young native girls in the first year after the katamenia. The anæmia gives the face a peculiar dull green colour which is masked by the pigmentation of the skin. Some of these cases have spoon-shaped nails (koilonychia) with stomatitis and dysphagia—the so-called Plummer-Vinson syndrome (*see p.* 488).

Lymphatic leukæmia and *spleno-medullary leucocythæmia* appear to be not as frequently as in Europe.

The position of *pernicious* (*Addisonian*) *anæmia* is by no means so well d ned. It appears to be a disease of northern peoples and is either or unknown in the tropics and subtropics. Wilkinson states that it not occur in South China. De Langen and Lichtenstein assert that they have never seen it in the course of their extensive studies in Java; it is said to be very rare in Ceylon and in South Japan. In Central Africa no cases are found in negroes. A diagnosis of pernicious anæmia should not be established without proof of achylia gastrica and megalocytosis, the latter ascertained by sternal puncture.

Thrombocytopenia vera is not uncommon in South China, and is undoubtedly to be found in many native races (*see* Onyalai, p. 673).

Diseases of the Heart and Blood-vessels

Valvular heart disease in the tropics is usually syphilitic. Williams (1938) in Uganda found that syphilis accounted for 53 out of 94 cases of heart disease and that syphilitic heart is five times as frequent as any other cardiac condition; aortic syphilis (aortic regurgitation) was found in 86 out of 894 post-mortem examinations. The average age of onset of symptoms in natives is forty-one years, i.e., considerably earlier than in Europeans. Macfie and Ingram (1920) found cardiac aneurysm very frequent on the Gold Coast. Aneurysms, often multiple, are extremely common in the Chinese, and rupture is one of the most frequent causes of sudden death.

Rheumatic valvular disease is a subject upon which much more precise information is required. W. T. James had never seen a case in twenty-four years' practice in Panama, and J. T. Clarke, in a series of 150,000 patients in Malaya, had the same experience. There is some evidence (*see* p. 38), that rheumatic infection does occasionally occur. Chesterman has seen typical rheumatic hearts at autopsy on the Congo. Sclerosis of the coronary vessels appears in normal frequency with advancing age, as in Europeans, but it is a curious fact that the clinical syndrome of angina pectoris is usually absent. Formerly it was believed that arterio-sclerosis was peculiar to the educated European classes, but recent researches indicate that, whenever the age is taken into consideration, there is practically no difference in vascular changes, which are at least as common in warmer countries as in the colder. Hyperpiesia appears to be practically absent in poorer natives living on a carbohydrate dietary, though Wilkinson finds it common in South China, tending to increase with westernization of habits. It should be observed that the normal blood-pressure, systolic and diastolic, in natives in the tropics, owing to smaller intake of protein, is 10–15 mm. of mercury lower than the normal in Europe. In those suffering from subnutrition, it is lower still.

The juvenile form of thrombo-angiitis obliterans (Bürgher's disease) appears to be common in native races and especially amongst the Southern Chinese.

Diseases of the Kidney and Genito-urinary Tract

Vesical and *renal calculi* are amongst the most common conditions encountered in the tropics, the former being the more frequent, especially among boys and young men. Little is known of their exact causation. By some the explanation is thought to lie in the high concentration of the urine; by others in an unbalanced dietary with lack of vitamin A. Urinary calculi are specially common in South China. Where urinary bilharziasis is common (Africa), the eggs of *Bilharzia hæmatobia* frequently form the nuclei of calculi.

Acute nephritis (acute glomerulonephritis) is commonly encountered, and is attributed to septic intoxication. De Langen and Wilkinson remark upon its frequency, especially in conjunction with scabies and with superadded septic infections. The clinical picture of contracted kidney with accompanying cardiac hypertrophy and hyperpiesia is rarely seen in indigenous natives, but in those who have adopted European habits, and in Chinese and Europeans in the tropics, it appears to be as common as elsewhere. The rarity of granular kidney is possibly correlated with the simpler diet and its low protein content. Chronic nephritis is especially common in South China.

The clinical picture of *nephrosis* (F. von Müller) is frequently seen. This is characterized by extensive and widespread œdema, and a high, but usually variable, albuminuria. There is a low total protein in the blood, and an inverted albumin-globulin ratio with increased cholesterinæmia. The urea and residual nitrogen are unchanged, whilst the blood-pressure remains normal without effect upon the heart. Nephrosis has often a syphilitic basis, and may be seen together with *quartan* and *subtertian* malaria (*see* p. 63). When all the causes are considered, there still remains a considerable proportion of cases without ascertainable ætiological basis, though many are found in association with ancylostomiasis.

Gonorrhœa, with its accompaniments, is one of the most common and widespread infections throughout the tropics. No one can estimate the extent of its prevalence or the disability that it causes. Not only is it responsible for joint and eye affections, but also for much serious disease of the female genitalia. Blacklock, in a thorough medical survey of Sierra Leone in 1930, estimates that 50 per cent. of males over fourteen have active signs and symptoms of this infection.

DIABETES AND GLYCOSURIA

It has long been believed that true diabetes (*diabetes mellitus*) is very common in all parts of the tropics. This opinion is based mainly upon the high carbohydrate consumption. The fact is that sugar (or substances which reduce Fehling's and Benedict's reagents) is comparatively often found in the urine amongst the Europeans and better-class natives in the tropics, but seldom in natives of the poorer class. De Langen, for instance, states that the incidence of diabetes in the Javanese is about 1 in 11,000, i.e., less than 0·01 per cent.

In British India also, diabetes is found among the richer people. Its comparative rarity in poorer natives is possibly to be ascribed to their shorter expectation of life. Diabetes usually develops in patients of riper years—those over fifty—and this factor may play a considerable part in statistical records. The relationship between obesity and diabetes is probably also important. Obesity is seldom seen in the average native, but among the rich, who can indulge more freely at table, a relatively higher incidence is observed.

The large number of cases of *benign glycosuria* in the tropics is remarkable, and these include the condition known as "renal diabetes." In this condition the blood-sugar content should not rise above normal. Patients with benign glycosuria feel perfectly well and show none of the usual symptoms of diabetes. The outlook in renal diabetes is favourable and the expectation of life is not affected.

GENERAL DISEASES

Gout.—It has always been held that there is a close connection between gout, obesity and overeating. It is also agreed that during the last half-century the incidence of this disease has almost everywhere decreased. It is always assumed that gout is very rare, or indeed non-existent, among tropical natives. Certainly it is seldom, if ever, observed in primitive peoples, and then only in those who have adopted European habits and customs. The Mahomedans suffer occasionally, while the Hindoos are said to escape entirely. In Manson's time gout was very rare in China, and in his diary he recorded one instance of gouty concretions in a Chinaman as an event of great importance. De Langen states that it has occasionally been observed in Java and the East Indies, but records in British India and in Central Africa are quite exceptional. Gout is said to be unknown in Egypt and in all the countries along the northern shores of Africa.

Arthritis.—Arthritis, including the infective and rheumatoid forms, occurs in native races, but to nothing like the same extent as in Europeans in temperate climates. Exact figures are very difficult to procure, as it is necessarily very difficult to exclude gonorrhœal arthritis. The available information has been included by McKinley in a table which purports to give the relative figures of incidence in various tropical and subtropical countries, but it is doubtful if the figures can be considered really reliable. In Ceylon, for instance, the number reported annually is given as 4,029, and the figure of 2,828 for the whole of India can hardly be considered accurate.

Acute articular rheumatism.—This apparently exists all over the world, but infrequently in native races, especially where the climate is hot and dry; consequently, the incidence of rheumatic valvular disease of the heart is correspondingly rare. There are those who state that they have never seen rheumatic fever or endocarditis in a lifelong experience in India, Malaya and Central Africa. Thus, Mackinnon states that chorea is never seen in East African children. Fernando in Ceylon, however, from extensive clinical and pathological observations, found that rheumatic infection is an important cause of carditis and accounts for one-quarter of the total number of cardiac cases. Wilkinson has testified to its presence in South China. On the other hand, Chesterman on the Congo found it very rarely in the native population, and it has been recognized in African children on the Gold Coast and in Nigeria, where it occasionally leads to mitral stenosis. Although acute rheumatism has been noted with normal frequency in European residents it is difficult to obtain more accurate information from the meagre data available.

DISEASES OF THE RESPIRATORY SYSTEM

Tuberculosis.—It has gradually been recognized that the extent of tuberculosis in the tropics is much greater than was formerly thought possible. The rapidity of spread and malignancy of course of pulmonary tuberculosis when first introduced into the Pacific Islands have been fully realized, and are well described by Robert Louis Stevenson among the Marquesans. Similar disasters have occurred in Samoa, Tonga and other Pacific Islands. In India, Rogers (1919) found no less than 9 per cent. of deaths due to tuberculosis, and Megaw estimates that, in the whole country, two million people are suffering from it. Scott has drawn attention to the pathological peculiarities of tuberculosis in Southern China. It has proved to be one of the main causes of death in Jamaica, the Gold Coast, the Philippines, on the Congo, and in Tanganyika, where it has been studied by Wilcocks.

For the rapid spread of the disease, its virulent nature, and the poor resistance offered by primitive peoples, several factors are responsible. Usually the patients do not come for medical treatment until they are in an advanced stage. The sputum is loaded with bacilli and, living as they do in primitive huts or houses crowded together, infected natives are a constant source of danger to their fellows. Spitting is a universal habit, and undernutrition and co-existing malarial and parasitic infections render them all the more susceptible.

The most important factor in the epidemiology of tropical tuberculosis is contact. Natives are able to resist a first infection but, once the disease has become established, their resistance is low. During the last ten years there has been an enormous increase in reported cases ; in some instances, as in Nigeria and British Guiana, it has been five- and six-fold, especially in the mining areas.

Unfortunately, tuberculosis is a disease which spreads with civilization, e.g., it was unknown many years ago in the Cameroons and in the southern Sudan. In Hong Kong, Scott, in an average of 4,000 autopsies a year, found marked tuberculosis in 5 per cent., and of these, three-fourths were children under ten. Tuberculosis among natives may be divided into two types, viz., "*natural*" tuberculosis, characteristic of those not immunized in any way against the disease, as in laboratory animals ; and "*modified*" tuberculosis, a more chronic condition, so called because it is modified by primary infection.

It appears to be generally agreed that hæmoptysis is not a prominent sign of tuberculosis in native children, though extraordinarily frequent in adults. Scott has asserted that, however extensive the disease, however large the cavity, he has never seen fatal hæmorrhage in a child. Spontaneous pneumothorax is found, but amyloid disease in chronic cases is very rare. Bovine tuberculosis, though it occurs, does not appear to be common.

Intestinal tuberculosis and tuberculous peritonitis are especially prevalent in China, and bone tuberculosis in West Africa. Recent writers have all stressed the importance of the nutritional basis as a factor of the first magnitude in the spread of tuberculosis in native populations.

Pneumonia.—Pneumonia, a principal cause of death almost everywhere in the tropics, especially in those countries with a persisting high humid atmosphere, has one of the highest mortality figures. Epidemics are specially found where native labourers are gathered together in compounds and in mining camps. The cause of the disease is usually a pneumococcal septicæmia, with little localization in the lungs. The clinical picture—rapid onset, extreme prostration and absence of the sthenic signs and symptoms which characterize the disease in Europeans, and of a termination by crisis—differs very considerably from that seen in temperate zones. All these factors impart a varying clinical picture and confound the newly-arrived doctor in the tropics. The story of pneumonia and its ravages in the Rand Mines and in the copper belt of Northern Rhodesia is familiar to students of this subject. It is in the treatment of pneumonia in tropical natives that sulphonamides, especially sulphapyridine, appear to be having their greatest triumphs.

ZYMOTIC DISEASES

Scarlet fever (scarlatina).—All observers agree that scarlet fever either is never seen in the tropics, or is very rare. De Langen, in the Dutch East Indies, asserts that such cases as have been tentatively diagnosed eventually prove to be something else. Fischer and others who have looked for it amongst the negroes of Central Africa have never found it. Probably the disease exists on the Gold Coast and Nigeria in such a mild state as to be unrecognizable, and the rash may be almost invisible on a dark skin (Gillespie).

Application of the Dick test to a selected number of tribes in Tanganyika showed a certain percentage of positive reactions, equal only to about one-third of the figure usually observed in Europeans; the few cases reported from Central Africa have all been among European residents. Bötticher (1934) has compiled a review of this subject. In South America and the West Indies, on the other hand, the disease occurs in sporadic outbreaks. In India, too, it is known, though rare; it is of a mild type and specially apt to attack small children. According to Megaw and das Gupta, from 1923 to 1926 scarlet fever was reported from 212 districts, but nearly all cases were European residents. It is common in North China, though it does not occur in the south. Jensen (1940) states that in China and the Pacific Islands scarlet fever is newly imported, and that the nearer to the equator the less is the morbidity and mortality. Zöller (1925) found that the Dick test gave uniformly negative results.

Measles.—Measles is widespread throughout all tropical countries and runs the same course as elsewhere, and the malignant type is not uncommon. Where no inherent immunity towards the virus exists, as in the Pacific Islands (especially Fiji and Rotumah), a measles epidemic may cause a high mortality in adults as well as children; thus in 1874 over 25,000 Fijians died from this disease. The measles rash has to be distinguished from that of typhus and dengue, but its appearance, though modified by a dark skin, is quite characteristic.

Diphtheria.—Diphtheria appears to be widespread and occurs in epidemic form, often when least expected. It is a disease of civilization and is evident only in towns and centres of population. It is recorded in the epidemiological statistics of most countries, with the exception of Africa. Whereas it is common in the northern and southern subtropical portions, it is apparently very rare in the tropical zone, and even at the present day in East Africa, Uganda, Tanganyika and in West Africa only. sporadic cases are discovered.

Mumps.—In the tropics this may be a generalized disease and assume a malignant form. In one-third of the cases orchitis is a complication. It is stated that the virus attacks the central nervous system, causing changes in the cerebrospinal fluid. Patients suffer from hallucinations and delirium—sometimes also they show Kernig's sign, bradycardia and ocular symptoms.

DISEASES OF THE CENTRAL NERVOUS SYSTEM

Syphilitic diseases of the central nervous system, such as tabes and general paresis, are seldom observed in Central Africa and the Pacific Islands, and this observation has been made the subject of much comment. In South China they constitute the commonest form of nervous disease.

Disseminated sclerosis is rare in most native races, and is not encountered in the Chinese.

Epidemic *encephalitis lethargica* (Economo's disease) has been noted in epidemics in Sarawak and in Cochin China (Bonnaire).

Epidemics of *anterior poliomyelitis* (infantile paralysis) occur in most tropical countries, notably in Kenya and Uganda, so that contact infections are by no means infrequent in Europeans.

Cerebrospinal meningitis occurs often in large epidemics, especially in the southern Sudan, where sulphapyridine has achieved remarkable results.

GOITRE

Simple parenchymatous or *colloid goitre* is extremely common in Egypt, in the Nile Valley, Sierra Leone, in the Caji districts of the French Congo, and in the Ouelle and Katanga districts of the Belgian Congo. It has been reported in the Dutch East Indies, especially in the Island of Bali. In India it is most common in the Himalayan and Subhimalayan regions and in the parts drained by the great Indian rivers (McCarrison), as well as in the western provinces of China. Disorders of secretion resulting in exophthalmic goitre, myxœdema or cretinism are almost unknown.

It has been remarked that goitre is not found among the Bedouin or other desert tribes. In endemic goitrous districts iodine should be given to all girls between the ages of eleven and sixteen and to all pregnant women.

MALIGNANT GROWTHS

There is no truth in the oft-quoted popular statement that malignant growths are unknown, or are very infrequent, among primitive peoples. The truth probably is that, age for age, they are as frequent as in civilized communities. The absence of accurate vital statistics, age records, or even registers of births and deaths, make such a comparison difficult. There are, however, certain special features of malignant disease amongst natives.

The outstanding facts about malignant growths in the tropics may be stated categorically as follows :

(1) The prevalence of primary liver carcinoma (12 per cent. of all carcinomata according to Vint), in 90 per cent. of cases

grafted upon cirrhosis (Snijders). (Cazanove in French West Africa, Snijders and Straub in Sumatra, Strachan in South Africa, Smith and Elmes in East Africa, French observers in Dakar, Senegal.) In China (Snapper) primary carcinoma nearly always arises in a cirrhotic liver. Malignant changes in the bile ducts are far less frequent, but may be associated with *Clonorchis sinensis* infections (*see* p. 757).

(2) The infrequency of gastric carcinoma.

(3) The prevalence of malignant tumours on the sides of the neck.

(4) The prevalence of skin carcinoma on legs and feet (grafted on chronic ulceration).

Many observers in recent years, especially Snijders, Straub and de Langen in the Dutch East Indies, Vint in East Africa and Rogers in India, have drawn attention to the fact that cancer should not be regarded as necessarily a scourge of civilization. Nor is it correct to state that the number of sufferers is increasing at a staggering rate. It was Hoffman, in compiling statistics for the United States Prudential Societies, who stated that the cancer rate was eight times as high amongst the 500 million of civilized races as among the 1,200 million uncivilized, including India; but Rogers's statistics, based upon 1,600 post-mortems in Calcutta, critically arrayed, showed no greater incidence of cancer in England than in India. The carcinomata were equally divided between the squamous and glandular epithelial forms, but the frequency of epitheliomata of the jaws in Calcutta is notable, and has also been recorded by French observers in Dakar, Senegal.

Malignant tumours, including both connective tissue and epithelial types, are about equally common in Bengal and in England, with a slight excess in the tropical country; but both innocent and malignant connective-tissue tumours are considerably more common in Bengal than in England. Vint has shown that, as far as Central Africa is concerned, there is close agreement between figures for malignant disease in natives, both in Nigeria and in Kenya. The large number of squamous-celled cancers in the latter country is due to malignant changes in chronic tropical ulcers of the legs, and to epitheliomata associated with this condition.

Carcinomata of the œsophagus and nasopharynx are especially common among the Chinese.

A further peculiarity is the relatively high proportion of sarcomatous to carcinomatous growths. In the extensive series of 5,000 autopsies from the Dutch East Indies, malignant growths were found in 9 per cent., and the proportion of sarcomatous to cancerous tumours was 1 : 8·9, whereas in Europe and America it is 1 : 10. Sarcomata of the very malignant round-celled type greatly predominate.

Malignant disease of the breast is not uncommon in the East African native and, according to Vint, in almost 20 per cent. of cases it is found in males. Sequeira and Vint have pointed out that malignant melanoma, next to squamous-celled cancer, is the commonest form of malignant disease in the natives of East and Central Africa, and O'Connor has stated that in Bengal melanotic sarcoma is distinctly commoner than in Europe. Most of the tumours are found on the foot, and the majority are on the plantar surface. Trauma is the most probable cause, as both sexes walk barefoot, and in a few instances " crab yaws " is an antecedent. The disease is usually locally malignant.

The clinical course of malignant growths differs, as a rule, between natives and Europeans. Through ignorance or fatalism, native patients resist to the very end before asking for medical aid, and are in a hopeless condition when discovered.

There still remain certain other peculiarities, consequent on local habits and customs. Thus Spittel, Davidson and Turner have shown that cancer (epithelioma) of the cheek is the commonest malignant growth in Ceylon, and is as frequent in women as in men between the ages of thirty-five and fifty ; here, no doubt, it is due to irritation caused by betel chewing. In Travancore, South India, it is also common, so that out of 1,700 cases collected by Bentall it formed 70 per cent.

Kangri-burn cancer is mainly found in Kashmir and is encountered in the older men. In the Mission Hospital there no less than 84 per cent. of the operations performed are for this condition. Kangri is an earthenware bowl 5–6 in. in diameter, surrounded by basket-work and surmounted by a wicker handle. It is heated by wood charcoal, and is worn against the skin under a loose garment. The growths are commonly found on the inner side of the thighs and anterior surface of the abdomen, above or below the umbilicus. The heat given out by the kangri is estimated at 150–200° F. The growths usually commence in the scars of previous burns. There are no metastases.

Burrows, Molesworth, and many other observers in Australia, have drawn attention to epitheliomata of the face, especially in Scottish and Irish immigrants, attributed to excessive irradiation by the ultra-violet rays of the sun.

Section I.—FEVERS

Subsection A.—FEVERS CAUSED BY BLOOD PROTOZOA

CHAPTER III

MALARIA

Definition.—The term malaria includes all fevers produced by endocorpuscular parasites of the genus *Plasmodium* which give rise to periodic fevers accompanied by anæmia, enlargement of the spleen and deposit of black pigment in the internal organs. Somewhat similar parasites occur in birds, bats and monkeys. Malaria heads the list as the most formidable of tropical diseases, and in India it is estimated to be responsible for at least two million deaths a year.

History.—The characteristic malarial pigment was discovered by Meckel in 1847, the malaria parasite by Laveran in 1880. The mosquito-malaria hypothesis was formulated by Manson in 1894, and in 1897 Ronald Ross discovered malaria oöcysts in the stomach wall of anopheles mosquitoes (*A. stephensi*) in India; in 1898 he demonstrated the life-cycle of the allied parasite of birds (*Plasmodium præcox*), the infection being conveyed from one bird to another by the mosquito in the act of biting. Subsequently Grassi in Rome demonstrated a similar cycle of development of human malaria parasites in *Anopheles maculipennis*.

It then became clear that man constitutes the intermediary and the mosquito the definitive host of the malaria parasite. In 1900 Manson instituted two crucial experiments proving the correctness of mosquito-malaria transmission. Drs. Sambon and Low and Signor Terzi lived in a mosquito-proof hut during the most malarial months in the Roman Campagna and remained free from infection. At the same time anopheles mosquitoes fed on malarial patients in Rome were despatched to London where they were set to bite Dr. P. T. Manson and G. Warren, both of whom shortly afterwards developed malaria fever, and malaria parasites were demonstrated in their blood.

Geographical distribution.—*Benign tertian malaria* is very widely distributed in the tropics, subtropics and temperate zones, though found most abundantly in warm countries. It extends as far north as 60° (Lake Ladoga in Russia and Southern Sweden). Severe epidemics have been recorded in Denmark, Holland, and the Emden district of Germany. Until recently, as "ague" or "marsh fever," it occurred to a limited extent in Southern England. The carrier in Northern Europe is *Anopheles maculipennis*, var. *atroparvus*. In America it occurs as far north as 40° N. in the valley of the Sacramento. In the southerly direction it has been recorded from Queensland at 20° S., in Natal at 30° S. and in South America at 40° S., on the southern borders of the Argentine. This form of malaria rarely, if ever, originates at an altitude above 6,000 ft. (*i.e.*, in the Himalayas). Records at higher altitudes are open to doubt.

Though widespread in the tropics it is not common on the West Coast of Africa, and certain islands are free of benign tertian and all other species of malaria:—Barbados (though a small outbreak due to introduced *A. albimanus* was noted in 1927), Tahiti, Hawaii, Fiji, Samoa and other Pacific Islands and, until comparatively recent times, Mauritius and Réunion, but the two last are now fever-ridden through the introduction of anopheles of various species.

Ovale tertian malaria, identified in 1922, is a particularly mild form of fever with tertian periodicity and appears to occur for the most part in Central Africa, and is found in Sierra Leone, the Gold Coast, Nigeria and Uganda. A few infections have been reported from Turkmenistan, Palestine, Egypt, Mauritius, Venezuela, India and the Philippines.

Quartan malaria until comparatively recently appears to have been commoner in temperate latitudes than in the tropics. It is recorded from Central Europe, sparingly in the Mediterranean area—in Italy, Macedonia, Palestine—Iraq, South India and the Andaman Islands, and is the dominant form in South Ceylon (except in epidemic outbreaks), in parts of Malaya, in New Guinea and adjacent islands. In Africa it is found sparingly, especially in the central portion. In America it is rare in the West Indies, but common in Antigua, in Panama and Brazil. In Macedonia and the Caspian area the maximum incidence is from July to November, and in many localities it appears to be confined solely to children (from 2–10 years) as, for instance, in Salonika and the Western Solomon Islands.

Subtertian malaria is much more "tropical" in its distribution. It is limited by the mean summer temperature of 70° F. (21° C.) and a mean winter isotherm of 48° F. (5° C.). In Europe it is rare, except in the Balkans and the Danubian marshes, but in the tropics it is the prevalent form, wherever fever is specially virulent. This is especially the case in desert oases, and subtertian is the chief form found in almost the whole of West and Central Africa, Asia Minor and in parts of Malaya and Central India. In the American continent it was formerly abundant in Panama and at present constitutes a menace in North and Central Brazil. In 1920 subtertian malaria was imported into Central Russia by refugees from Turkmenistan and spread as far north as Moscow where cases occurred even during the winter season.

Epidemiology and endemiology.—Conditions which favour the presence and breeding of anopheles mosquitoes tend to the increase of malaria, and *vice versa*, and whatever favours access of these insects and the parasites they contain also favours the acquisition of malaria.

Special types of terrain are particularly malarious: the water-logged country of the foothills of high mountain ranges, the deltas of most large rivers (though the deltas of the Mekong and the Red River of Indo-China are relatively free). The pool-dotted beds of dried-up streams and recently deforested lands are notorious. On the other hand there are instances of elevated, arid and sandy plains which are dangerous. Malaria is a disease of the open country and villages rather than of towns. These circumstances are related to the distribution of anopheline mosquitoes which occasionally, under favourable conditions, increase and spread. New species may be introduced into an area, as has happened many times in the world's history.

In subtropical regions subtertian malaria is a primary infection in summer and early autumn, hence the popular term—*æstivo-autumnal* *fever*. This peculiarity can be explained to some extent by the higher atmospheric temperature required for its development in the mosquito. Hence, though benign and subtertian forms are frequently associated, and the latter can be acquired at any time in the tropics, it is only in the summer and early autumn that subtertian can be acquired in more temperate zones. When the temperature falls below 15° C. development of the oöcyst in the mosquito is arrested, but when once the sporozoites have entered the salivary glands, they are capable of infecting man, even during the winter season. There is no evidence that any particular type of malaria is associated with any particular species of anopheles. Generally speaking, the most important conditions necessary for the propagation of the benign tertian parasite are the *sustained* average temperature of at least 60° F. (15·5° C.) and a humidity of at least 63 per cent.

There are other factors to be considered. Wenyon explained the seasonal variations of the two dominant forms of malaria in Macedonia and Palestine by the fact that the benign tertian tends to relapse over a longer period and is more resistant to quinine, whilst the subtertian is more amenable to treatment and there is less tendency for infections to persist from one season to the next. Though the numbers of benign tertian and subtertian cases may be approximately equal in the height of the season, subtertian malaria more rapidly develops a heavy infection and produces a greater number of gametocytes ; thus, it tends to spread in epidemic form with greater rapidity.

The spread of malaria is also intimately related to the susceptibility of the human host. When health is impaired and resistance diminished by malnutrition (see p. 25) or by physical exertion, or undermined by co-existing disease such as tuberculosis, chronic dysentery or ancylostomiasis, the infection spreads more rapidly and tends to assume virulent and intractable forms. This was particularly noted in the great malaria epidemic of Ceylon in 1933–4 which, though mainly due to the benign tertian parasite, was responsible for over half a million deaths. Every circumstance tending to physiological depression favours susceptibility.

Immunity produced by previous infection is another consideration (*see* p. 84). D. B. Wilson states that subtertian malaria causes little illness in the adult Bantus of parts of Tanganyika, though all babies are infected in their first few months of life, and suffer severely before immunity is acquired.

A belt of trees between a malarial swamp and human habitations may filter out mosquitoes by affording them protection from winds. Open windows and doors are a danger in malarious countries and for this reason sleeping on the ground floor or unprotected by a mosquito-net is dangerous. The times just before sunrise and after sunset and the night are most dangerous, but, although most active during twilight and night, anophelines bite readily enough during the daytime in shady and windless places, in dark rooms and thick jungles. Very few species of anopheles are strictly diurnal.

As a rule, malarial infection declares itself a week or ten days after the infective bite of a mosquito. In some individuals the incubation period may be greatly prolonged ; the spring malaria in Holland, for instance, is thought to be due to infection acquired during the preceding autumn. Few individuals are, however, permanently immune. A malarial subject may remain in fair health while resident in the tropics, but when he is exposed to cold, wintry winds, as on an ocean voyage, or when excessively fatigued, latent malaria is likely to become active again and an attack ensue.

Ætiology of Malaria (Plate II)

The four species of parasite (*Plasmodium*) causing malaria in man differ from each other in morphology, but the general course of their life-history is similar. They all have two distinct phases: intracorporeal and extracorporeal. Each species has its special intracorporeal life-cycle that may last approximately 48 to 72 hours. The extracorporeal cycle is undergone in the body cavity of an anopheles mosquito.

The malarial parasite can be recognized in fresh unstained malarial blood an hour or so before a paroxysm; it is a pale disc inside the red blood corpuscle (Fig. 3, *a*), and at a later stage a number of fine black or reddish-black particles of pigment (*hæmozoin*, formerly known as *melanin*) are scattered throughout its protoplasm. This pigment is believed to be the excrement of the parasite. It collects, as the parasite grows, in central blocks round which the protoplasm becomes divided into segments (merozoites); when the cycle is complete the containing corpuscle (host cell) breaks down and liberates the spherules, none of which contain hæmozoin. This stage coincides with a clinical fever.

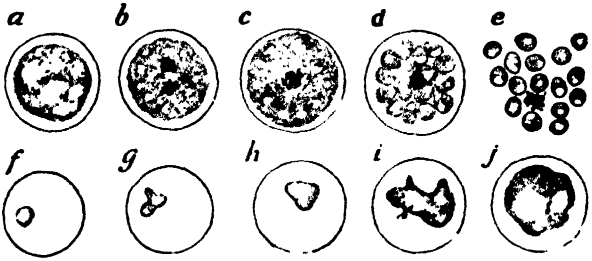


Fig. 3.—Evolution of the tertian parasite, unstained.

A number of these freed spherules escape phagocytosis by wandering leucocytes and attach themselves to other red corpuscles, enter them, and grow at the expense of the hæmoglobin, exhibiting active amœboid movements. When appropriately stained, the free merozoites are seen to consist of a nucleus surrounded by a rind of protoplasm; as they reach maturity a nucleolus becomes visible. (Fig. 4, *a*, *j*). In the pre-sporulation phase the nuclear elements become scattered throughout the protoplasm, and around them the segmenting parasite arranges itself to form merozoites (Fig. 4, *b*, *c*). The vesicular character of the nucleus does not become apparent in the merozoites until they lie free in the plasma. The hæmozoin or pigment particles of the malaria parasite are either black or dark brown dust-like specks, grains or rods, isolated or aggregated into more or less dense clumps. As long as the nucleus remains entire, the hæmozoin is peripheral, but when segmentation takes place it becomes central.

The *extracorporeal or mosquito cycle* commences with a process of exflagellation. This is a sexual phase which can take place in the blood after it has been withdrawn from the body. As observed in fresh wet preparations of blood, the flagellated body is derived from the male sexual cells or gametocytes, which are composed of protoplasm and hæmozoin and which possess, on more minute examination, a distinctive structure. These sexual cells are usually round, but in subtertian malaria (*P. falciparum*) they are crescentic. These well-known " crescents " become rounded off before flagellation. The flagella (more correctly, the microgametes) number from one to six or more. They are extremely delicate filaments, which move about rapidly and which every now and again break away and swim about with vibratile movement. Only the male cell (microgametocyte) undergoes this process ; the female (macrogametocyte) remains rounded and stationary until fertilized by one of the erupted flagella (microgametes). This event signalizes the first stage in the development of the malaria parasite in the stomach cavity of the anopheles mosquito. (For further details, *see* p. 849.)

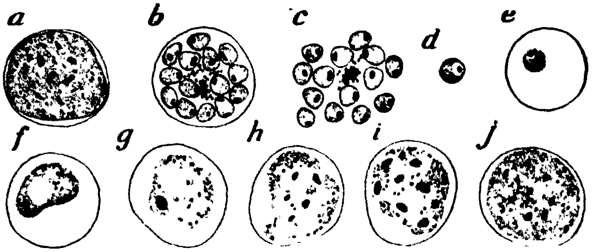


Fig. 4.—Evolution of the tertian parasite, stained.

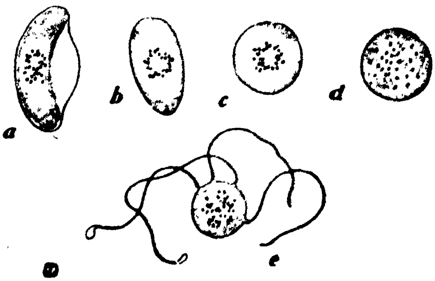


Fig. 5.—Evolution of the flagellated body from the crescent (male gametocyte).

Possibility of a latent phase of the malaria parasite in the human body.—It is a well-established fact that when the fever subsides the parasite disappears from the general circulation, either spontaneously, or as the result of the administration of quinine, atebrin or plasmoquine.

After an interval of weeks or months, however, the parasite may reappear in the peripheral blood. So far no satisfactory explanation has been given for this extraordinary latency. In benign tertian and quartan malaria it may be as long as nine months or a year after quinine, atebrin or plasmoquine treatment (*see* p. 99). Shute has suggested, from this and other evidence, that the sporozoites, when injected into the skin by the mosquito, do not all reach the bloodstream but may be held up in the skin for a long period. It is possible that there is an exo-erythrocytic cycle of development of the human malaria parasite in the endothelial cells of the spleen, liver, kidneys and capillaries. There is some evidence that this has actually been seen in man as described by Raffaele (1937) and Brug (1940). Confirmation, however, is lacking. This cycle certainly takes place in the plasmodia of birds (*see* p. 840).

Transmission of malaria by blood transfusion, drug addiction and salvarsan injections.—There is considerable risk of conveying malaria in the transfusion of citrated or stored blood ; *P. vivax* especially may be found in the blood of donors exposed to infection within four years before the transfusion. In London a case of fatal quartan malaria has been recorded in a baby transfused with compatible blood from its father who had lived in Ceylon twelve years previously and who had never suffered from any clinical manifestations of malaria (Nabarro and Edward). Gardner and Dexter have recorded a similar instance in which the interval was seventeen years.

In non-malarial countries persons who have had malaria should not be used as blood donors. In malarial countries this rule cannot apply, but it is probably safer to use blood stored for not less than eight days. If fresh blood must be used, the recipient should be given quinine or atebrin as a prophylactic, and the risks of transmission are reduced if the donor has taken quinine regularly. Dried plasma and serum prepared from malarial blood are safe.

Hutton and Shute demonstrated that malaria parasites may survive for days, or even weeks, in blood stored at low temperatures—about 4° C.

In Cairo, severe, and even fatal, subtertian malaria was recorded by Biggam in heroin drug addicts from indiscriminate use of unsterilized syringes containing congealed blood. Similar instances have been recorded in New York by Appelbaum, Gelfand, Helpern and Most, and especially on the Pacific Coast, as well as in Peking by Chung and colleagues. Boyd and Slackman stated that the mortality rate amongst drug addicts may be very high. Helpern recorded 49 cases, of which 27 died.

Similarly, virulent subtertian malaria may be transmitted by unsterilized needles in intravenous injections of salvarsan, as recorded by Wenyon (1918) and Black (1939).

Transmission of malaria to the fœtus.—Congenital malaria is rare, but undoubtedly occurs. Some have thought that there must in these instances be a mechanical tear, or placental hæmorrhage, by which the parasites gain entrance to the fœtal blood. Lopatin suggested intrauterine emigration of infected maternal erythrocytes into the fœtus as a result of damage to the maternal blood vessels. Or it may be that, as the result of overwhelming malaria infection, the placenta itself has undergone pathological changes. Blacklock and Gordon in Sierra Leone found malaria parasites in the maternal blood spaces of the placenta in 38 per cent. of parturient women; in no case were parasites found in the fœtal blood, yet of the children born with infected placentæ one quarter died within a week.

Buckingham has demonstrated malaria parasites in the blood of a premature child; Heiser found crescents of *P. falciparum* in an infant seven days old. Jones and Brown (1924) recorded an attack of benign tertian malaria in a child in Buckinghamshire 16 days after birth: the mother had an attack of fever during delivery. Tanner and Hewlett in London (1935) recorded a similar instance two months after birth, and in one of twins, and Hoo (1941) a somewhat similar case in Amsterdam in a breast-fed child fourteen days old, where the mother had been originally infected with benign tertian malaria. These examples outside the tropics are most convincing, especially in England, where the possibility of indigenous infection does not arise. Wickramasuriya in Ceylon found it comparatively common, and in three out of six proven cases of trans-placental infection death of the fœtus was attributed to malaria (*P. falciparum*) contracted *in utero*.*

The four forms of parasite and associated fevers.—There are four clinical types of malarial disease which are associated respectively with four distinct species of malaria parasite. These species have been classified according to: (*a*) the duration of their respective life-cycles inside the human body; (*b*) their morphological characters; (*c*) the clinical phenomena to which they give rise; and (*d*) the results of inoculation experiments.

Benign parasites are of three kinds: the *quartan*, which has a cycle of seventy-two hours and causes a fever that recurs every fourth day, counting from the first day of fever—*quartan fever*; the *benign tertian* parasite, with a cycle of 48 hours, causing a fever which recurs every third day, counting in a similar way—*tertian fever*; and the *ovale tertian* which in many respects resembles benign tertian. The malignant or *subtertian* is also known as the *æstivo-autumnal*, and has a life-cycle of approximately 48 hours (*see* Table I).

Inoculated or therapeutic malaria.—Following the work of Wagner-Jauregg of Vienna, the treatment of general paralysis of the insane and other grave nervous disorders includes the injection, subcutaneously or intramuscularly, of 1 to 2 c.c. of blood containing benign tertian parasites, with consequent production of attacks of malaria in the person thus injected. The best results are obtained with blood which has been immediately defibrinated and kept in a thermos flask at freezing-point. It is most important that *P. vivax* and *P. ovale* strains should be used; deaths have occurred from inoculation with certain strains of *P. falciparum*, though others in James's hands have proved beneficial. Favourable results have been recorded in Vienna from the employment of *Spirochæta duttoni* of relapsing fever in place of malaria.

Therapeutic malaria may also be produced by the bite of an infected mosquito or by the actual subcutaneous injection of the extract of the salivary

---

* A case of congenital benign tertian malaria in a child of one month, born in England, was y Gammie (1944).

PLATE II

MALARIA PARASITES. × 2,000

A.—SUBTERTIAN PARASITE (*Plasmodium falciparum*).

Fig. 1.—Subtertian rings. Note the marginal form and, in one, double chromatin dots.

Fig. 2.—Quarter-grown parasite. When seen in the peripheral blood this denotes a severe infection, as it normally occurs in the capillaries of the internal organs. Note discolouration of cell, its irregularity and the pernicious stippling—known also as "Stephens's" and "Christopher's" dots, also as "Maurer's dots" or clefts.

Fig. 3.—Schizogonic stage, or rosette form, with thirty spores, also usually in capillaries of internal organs—seldom seen in peripheral blood.

Fig. 4.—Male gametocyte (crescent).

Fig. 5.—Female gametocyte (crescent) showing concentration of chromatin and pigment.

B.—BENIGN TERTIAN PARASITE (*Plasmodium vivax*).

Fig. 1.—Young ring form.

Fig. 2.—Quarter-grown parasite. Note Schüffner's dots and slight enlargement of corpuscle.

Fig. 3.—Half-grown parasite. (Amœboid form).

Fig. 4.—Three-quarter parasite. (Amœboid form).

Fig. 5.—Presporulating stage showing fragmentation of chromatin.

Fig. 6.—Complete schizogony. (Rosette stage with 20–24 spores).

Fig. 7.—Male gametocyte. Note loose arrangement of chromatin and purple tinge of protoplasm.

Fig. 8.—Female gametocyte. Note compactness of chromatin and blue tinge of protoplasm.

C.—QUARTAN PARASITE (*Plasmodium malariæ*).

Fig. 1.—Ring form.

Fig. 2.—Quarter-grown parasite ("band form"). Note corpuscle is not enlarged.

Fig. 3.—Half-grown parasite ("band form"). Note the scattered black pigment.

Fig. 4.—Presporulating stage.

Fig. 5.—Complete schizogony. (Rosette stage with 8–9 spores).

Fig. 6.—Male gametocyte. Note purple tinge of protoplasm with heavy pigmentation.

Fig. 7. Female gametocyte. Note blue tinge of protoplasm. (Blue dots, when present in the blood corpuscle, are known as Ziemann's stippling).

Fig. 8.—Normal red blood-corpuscle for comparison of size.

D.—OVALE TERTIAN PARASITE (*Plasmodium ovale*). (*After James, Nicol & Shute.*)

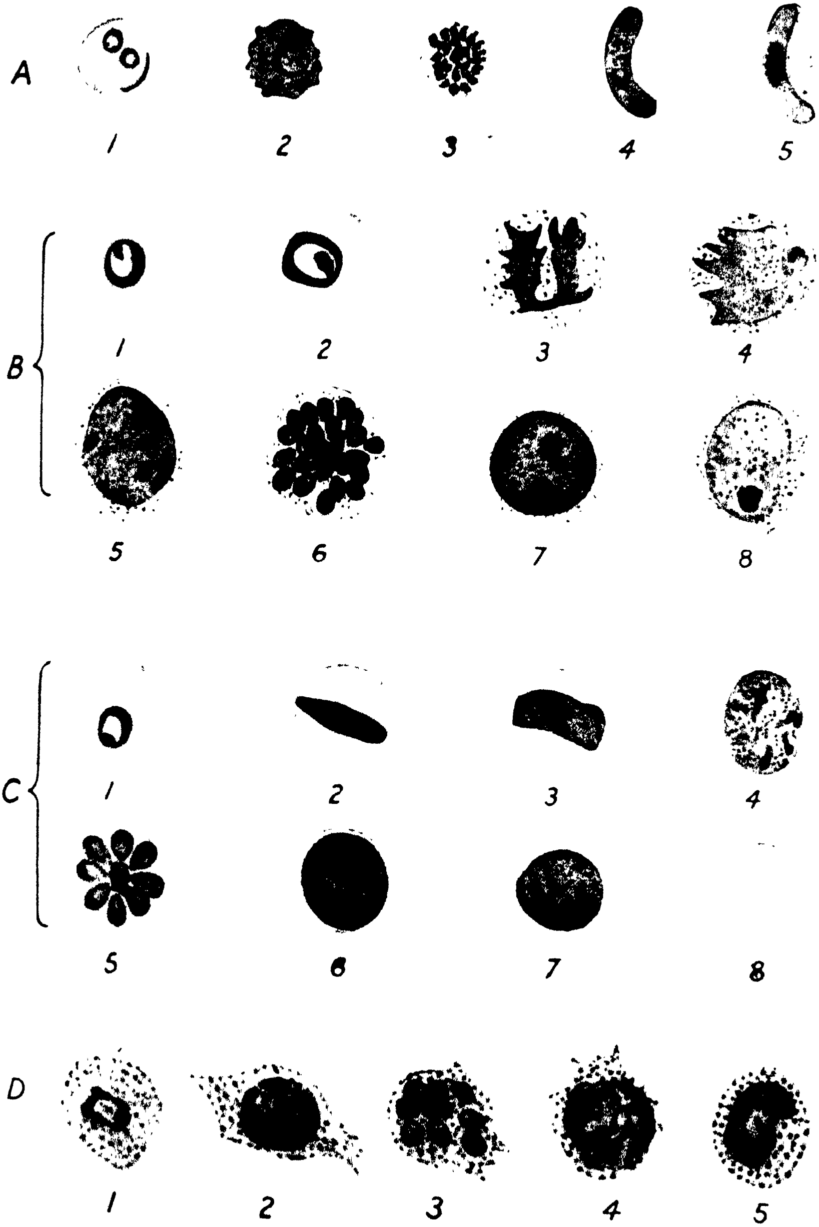
Fig. 1.—Ring form. Note Schüffner's dots.

Fig. 2.—Presporulating stage. Note irregular and oval shape of corpuscle with coarse and prominent Schüffner's dots.

Fig. 3.—Complete schizogony. Note irregular distribution and oval shape of spores, and also distortion of corpuscle.

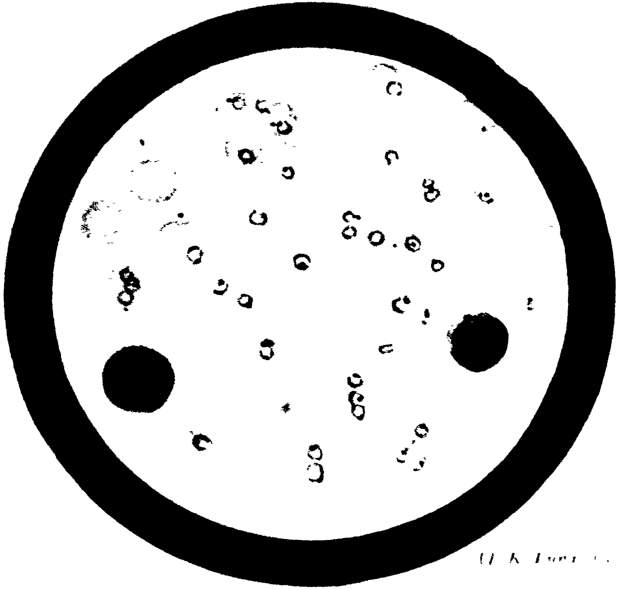
Fig. 4.—Male gametocyte. Note coarse Schüffner's dots and purple tinge of protoplasm.

Fig. 5.—Female gametocyte. Note marginal arrangement of pigment.



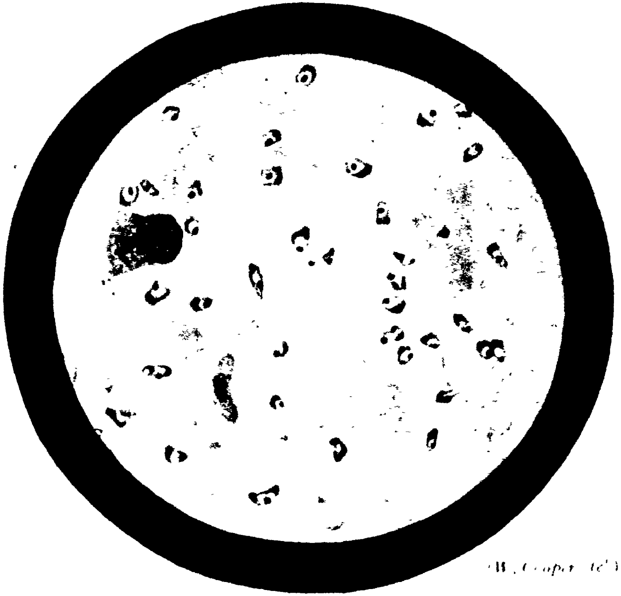
(P. H. Manson Bahr del.)

MALARIA PARASITES.



(J. K. Lowe del.)

Fig. 1. **Blood-film from fatal case of subtertian malaria, showing heavy "ring" infection.** *(Giemsa's stain.)*



(W. Cooper del.)

Fig. 2. **Thick blood-film preparation of subtertian rings and crescent stained by Leishman to show appearances after dehæmoglobinization.** × 1000. *(From a preparation by Dr H. Seidelin.)*

THE BLOOD PICTURE IN SUBTERTIAN MALARIA.

PLATE III

TABULAR STATEMENT OF THE CHARACTERS OF THE FOUR SPECIES OF MALARIA PARASITE

	Duration of schizogonic cycle	*Movement*	*Hæmozoin*	*Trophozoites*	*Adult schizont*	*Number of merozoites*	*Form of gametocytes*	*Alterations in corpuscles*	*Relative number of parasites in peripheral and visceral blood*	*Liability to relapse*
1. Benign tertian parasite, *Plasmodium vivax*.	48 hours	Active amœboid.	Fine, yellowish brown.	Signet rings of various sizes; growing forms irregular in size, with vacuole.	Larger than a red cell.	14-24, average 18-20.	Round or slightly ovoid larger than the red cell.	Hypertrophied and pale; stippled with Schüffner's dots.	Parasites numerous in all parts of the body in various stages of their cycle.	Relapses noted up to 3½ years from time of original infection
2. Quartan parasite, *Plasmodium malariæ*	72 hours	Slight, in immature forms.	Coarse, and dark brown.	Signet rings, as in *P. vivax*; growing forms bandlike or angular. Vacuole soon disappears.	Slightly smaller than a red cell.	6-12, average 8 or 9.	Round or slightly oval, size of red cell.	Not enlarged, may be slightly contracted; no Schüffner's dots, but sometimes Ziemann's stippling.	As in *P. vivax*.	Infection particularly persistent. Relapses may occur for 10-21 years or more from time of original infection.
3. Subtertian parasite, *Plasmodium falciparum* (*Laverania malariæ*).	24-48 hours (irregular)	Active amœboid.	Pigment blacker than in other forms; may be aggregated into coarse granules.	Rings small, often containing two clear granules, and sometimes attached to edges of red cell.	Distinctly smaller than a red cell.	8-24, sometimes more. Very variable.	Crescentic or sausage-shaped.	Usually unaltered; in later stages paler, sometimes containing coarse dots or irregular mottling (Maurer's dots or clefts).	The greater development of the parasite takes place in the internal organs; hence the relative scarcity of all, save most immature forms, in peripheral blood.	Much less than in other two forms; infection intense in early stages. Relapses rarely occur after 9 months from time of infection. Maximum period observed, 1½ years.
4. "Ovale tertian", *Plasmodium ovale*.	48 hours	Non-amœboid.	Blackish brown	Rings indistinguishable from those of *P. malariæ*.	Smaller than a red cell.	8-12	Oval, size of red cell.	Oval and irregular.	As in *P. vivax*.	Short-lived infection as a rule; may persist for 1½ years.

glands containing sporozoites. Contrary to the opinion formerly held, it has been shown that inoculation of sporozoites from the salivary glands of one infected anopheles will produce in some persons *quotidian* rigors due to parasites sporulating within a day of each other. In many cases, also, after an incubation period of 7–10 days, the onset of the malaria attacks is characterized, not by typical intermittent fever, as seen in Charts 1, 2, but by a *remittent fever* which may persist for a week or more before becoming frankly *intermittent* (Chart 3). This feature appears to have been noted in the historic inoculation experiments originally carried out by Manson and Grassi (p. 44). One objection to the use of benign tertian malaria is proclivity to quotidian fever, which is extremely exhausting to debilitated patients. Injections of thio-bismol, 0·2 grm., have been shown by a number of observers (Schwartz, Brunsting and Love, Cole, Whelen, and Shute) to have the property of destroying the half-mature schizonts of *P. vivax*, thus eliminating alternate cycles, and of transforming a quotidian into a tertian fever. (Thio-bismol is the trisodium salt of bismuth thio-glycollic acid $\mathrm{Bi\ (SCH_2\ Co_2\ Na)_3}$ and contains 38 per cent. metallic bismuth.) The optimum time for injection is about the fourth day. During the incubation period it has no effect. The results of therapeutic malarial treatment have, according to Yorke and Macfie, been favourable: 27·4 per cent. of general paralytics were regarded as temporarily cured, while in a further 20·2 per cent. great physical and distinct mental improvement was observed. It has been proved that stabilization takes place so that re-adaptation to family life and social responsibilities is possible. In other forms of cerebro-spinal syphilis, it seems as if malaria therapy acts as a mordant for specific medication.

In inoculated infections disinfection by quinine or atebrin is extraordinarily easy. To effect a complete cure, the amount of quinine administered varies from 45–150 gr. and about 3 grm. of atebrin. Relapses after subcutaneous inoculation of malaria are extremely rare, while in naturally-acquired malaria they are common. It seems, therefore, that malarial infection produced by the injection of sporozoites is much more long-lived and much less amenable to quinine. Valuable information about the failure of quinine to act prophylactically has also been obtained. The administration of quinine in 10 gr. solution daily for five days before, on the day of, and eight days after the bite of infective mosquitoes fails to prevent the development of malaria; similar results have been obtained in cases where 30 gr. in solution were given on the day of feeding infective mosquitoes and on each of the two following days. These experiments show that quinine has no action upon sporozoites injected by the mosquito; on the other hand the development of malaria can be prevented by 10 gr. of quinine daily taken for ten days after the infecting bites.

Artificial infection of susceptible species of anophelines, and technique employed.—For the production by mosquito bite of malaria infection in general paralytics, wild-caught mosquitoes obtained in country districts free from malaria may be used, but it is now usual to breed them in insectories, allowing them to obtain blood meals from pigs. The insects are collected one by one in a test-tube and transferred to a mosquito cage. When about 300 have been caught, a waterproof cover is drawn over the cage, which is then taken to the laboratory. After removal of the cover, the cage is placed in an incubator at 23° C. for twenty-four to forty-eight hours in order that blood in the stomachs of the mosquitoes may be digested quickly and that they may be ready to feed upon the infecting case. It is essential that the peripheral blood should contain male and female gametocytes in the ripe stage; the male forms should "flagellate" readily in a moist-chamber preparation of freshly-drawn blood (*see* p. 1001).

In artifically-inoculated malaria cases, in order to produce, for example,

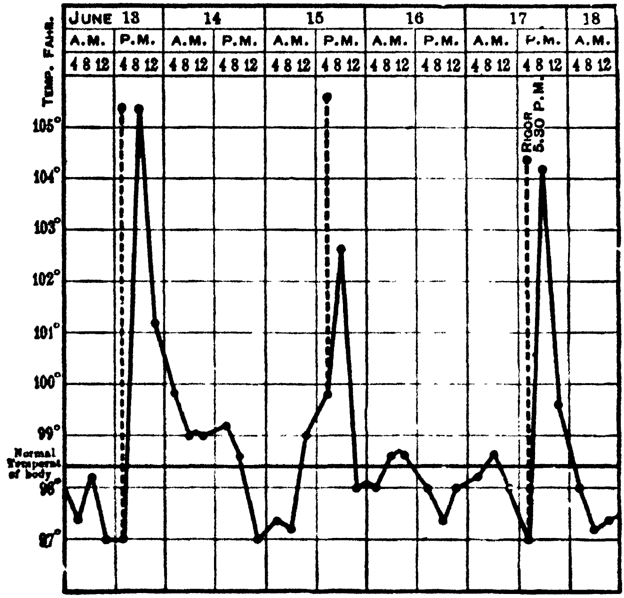


Chart 1.—Benign tertian ague.

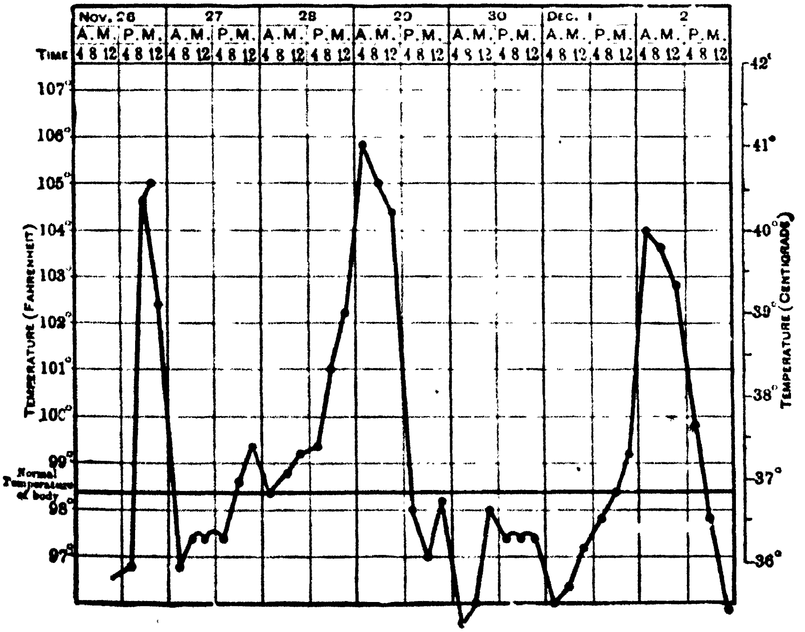


Chart 2.—Quartan ague.

a sufficient number of gametocytes of benign tertian, James finds it best to permit the patient to have a number of (ten or more) attacks of malaria before administering a small dose (5 gr.) of quinine. A remission of fourteen to seventeen days will occur before the next attack, when gametocytes in the right stage should be abundant in the peripheral blood.

When the mosquitoes are to be fed on the infecting cases they are taken from the cage in a test-tube and transferred to glass jars. The tops of these jars should be covered with a piece of paper in which a half-circle valve of the same size as the mouth of the test-tube is cut. To liberate the mosquitoes the cotton-wool plug is withdrawn from the mouth of the test-tube at the same time that it is pushed through the valve. When the mosquito has flown into the bottle, the tube should be withdrawn and the valve plugged with cottonwool. After twenty mosquitoes have been transferred to each of four or five bottles, pieces of mosquito-netting should be laid over the paper which closes their mouths and, holding the mosquito-netting in place with the palm of the hand, the paper should be carefully drawn away, leaving the netting as a cover, which should then be tied on tightly.

The jars containing the mosquitoes are then placed on the leg of the patient. An attendant should keep the mouths of the jars pressed closely against the skin during the period allowed for feeding, which is usually about twenty minutes. The mosquitoes bite readily through the netting, but when they have fed, the jars are placed inside the cage and the netting covers removed, when they escape into the cage. This is kept in an incubator at 23° C. (73° F.) and, by standing a bowl of water in it and hanging wet cloths around it, the air is kept as nearly saturated with moisture as possible. The procedure is repeated daily, the mosquitoes being fed for at least five successive days

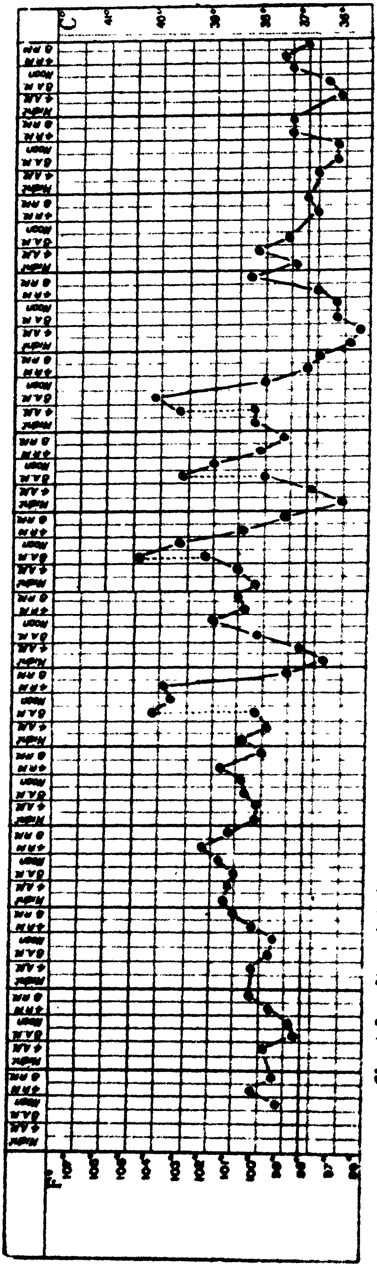


Chart 3.—Inoculated benign tertian malaria, showing initial remittent pyrexia. (*Dr. G. C. Low.*)

on an infecting case. Afterwards they are fed every day, or every other day, on a patient who is awaiting treatment, in order to ensure that they obtain the necessary amount of nutriment. Some mosquitoes die every day, and these are dissected to ascertain the progress of the malaria infection. When sporozoites are present in the salivary glands (usually between the tenth and fifteenth day after the first infective feed), incubation is discontinued and the group of insects should be kept either at room-temperature or in an icebox at 5° C., when further development will be arrested and the mosquitoes will remain torpid, but ready to infect a patient whenever required.

To infect a patient, four or five mosquitoes are transferred from the cage to one of the glass jars and allowed to bite. Usually two or three bite within a few minutes. When human blood cannot be obtained to nourish the mosquitoes, they can be fed on glucose solution sprayed on cotton-wool.

By this method James has shown that nearly 100 per cent. become infective; while the experience of Wenyon in Salonika and that of the Editor in England shows that after a single feed on a suitable benign tertian case fully 80 per cent. of *A. maculipennis* develop oöcysts in their stomachs provided that the air is kept moist and warm.

MORBID ANATOMY AND PATHOLOGY OF MALARIA

Spleen.—The spleen is big and, when grossly enlarged, is popularly known as the "ague cake." Although it fluctuates in size it is most certainly *always* swollen during an acute attack. The surface is dark, sometimes almost black and, on section, is dark-red, purple or chocolate-black from congestion and pigmentation. In subtertian infections (which account for the majority of fatal cases) the parenchyma is so softened as to be almost diffluent, the capsule being tightly stretched like a bag of congealed blood. The pulp is so tarry that it can be washed away by a gentle stream of water; it is diffluent and the Malpighian bodies appear pale grey. Such an enlarged spleen can easily be ruptured and cause death. Its weight varies enormously according to the duration and intensity of infection. Clark estimated the normal spleen in negroes at 140–160 grm. (5–6 oz.) and says that it must exceed 300 grm. (11 oz.) before it can be reasonably detected by palpation during life. There may be few signs of perisplenitis.

Histologically, half-grown parasites and a few pigmented monocytes are seen in branches of the splenic artery. Areas of thrombosis and hæmorrhage, small local infarctions and necroses occur from blockage of the vessels, as well as from toxic action. No pigment is seen in the Malpighian bodies. The venous sinuses are greatly dilated; the endothelial cells contain pigment and histiocytes with ingested pigment, red cells and phagocytosed parasites. Especially in subtertian infections, these parasitized cells in the capillaries tend to adhere to the endothelial cells and may actually block the lumen.

In the interval between attacks hyperæmia disappears and the organ becomes more solid, harder, and shrinks. In this state the Malpighian bodies may diminish in size and stand out sharply against a dark background, and the pigment is scattered throughout the organ instead of occurring in clumps as during an acute attack.

Liver.—The liver is usually congested, enlarged, pigmented and olive-brown, especially in the left lobe which receives the splenic blood. Glisson's capsule, surrounding the portal system, is stretched.

Histologically the appearances vary widely, according to the intensity of the infection. The parenchyma cells do not take up the malaria pigment, but they contain the product of its destruction, hæmosiderin, and also bilirubin. (*Hæmosiderin* contains ionizable iron; hæmozoin (malaria pigment) contains non-ionizable iron, so that the former does not give the Prussian blue reaction with potassium ferrocyanide, unless acted upon first by nitric acid and hydrogen peroxide). The sinusoids are congested and the Kupffer cells contain hæmozoin; the parasites (subtertian) are present in the sinusoids, and changes are most marked at the periphery of the lobules. Parenchyma cells show all stages of degeneration owing to interference with the blood supply, the presence of toxins and, in very acute infections, there may be widespread areas of necrosis around the central vein. Usually, the cells show cloudy swelling with granular contents and diffusely staining nuclei. Little hæmorrhagic areas are seen in the vicinity of focal necroses.

In chronic malaria the slaty-grey colour is due to pigment deposits. The organ is more solid from an increase of the endothelial cells, but pigment is still located mainly in the outer zones of the lobules, but is also seen in the histiocytes and the connective tissue of Glisson's capsule.

Kidneys.—In acute cases of malaria there is great congestion, without pigmentation, but grey dots and lines can be distinguished in the pyramids of the cortex. The small dots represent Bowman's capsules which are full of agglomerated parasitized red corpuscles. There is considerable damage to the convoluted tubules, especially the first, and degenerative changes in the epithelial cells with loss of outline and feebly staining nuclei—a process which may proceed to complete necrosis. In severe subtertian infections the lumen of the tubules is filled with granular casts and sometimes there are actual hæmorrhages; the changes may then amount to a parenchymatous degeneration. The kidney appears to be especially affected in severe subtertian and quartan infections.

Heart.—In subtertian infections this organ is especially picked out. The blood vessels are packed with parasitized cell masses; there is fatty infiltration of the cardiac muscle fibres and subendocardial petechial hæmorrhages.

Lungs.—Congestion of alveolar capillaries is seen, and the vessels are blocked with parasitized red and macrophage endothelial cells. The pleura and lung tissue are grey from deposited hæmozoin. All these changes interfere with the natural resistance so that malaria-infected subjects are more liable to pulmonary disease.

Pancreas.—There is often focal necrosis due to blockage of the capillaries, especially of the nutrient vessels of the islets of Langerhans, and in rare instances the clinical appearances of an acute hæmorrhagic pancreatitis may be reproduced.

Suprarenals.—These too are especially attacked in subtertian infections. There is partial or complete loss of the yellow colour (lipoids) of the cortex and congestion and blockage of vessels with parasites. The implication of these endocrine glands is held to be responsible for algid symptoms observed during life.

Stomach and gastro-intestinal tract.—The mucosa is coated with mucus and there is gastro-intestinal catarrh. Therefore, achlorhydria is common in the acute stage of malaria, and this may account for the dyspepsia and gastro-intestinal irritation. The blood capillaries are loaded with parasites, and degenerated areas of mucous membrane are encountered which may give rise to dysenteric symptoms.

Bone marrow.—The yellow and adipose tissue is very vascular and the red marrow is dark or chocolate brown, especially at the periphery. Considerable phagocytosis occurs, with pigment-containing macrophages. Parasitized cells are present in large numbers, especially immature crescents. There is myeloid hyperplasia with many normo- and megaloblasts. In chronic cases the marrow is redder and more solid, and the fat disappears.

Central nervous system.—The brain is normal except in cerebral subtertian cases, when it has a leaden hue due to deposition of malaria pigment and parasitized cells in the capillaries. Often there are punctiform hæmorrhages in the subcortical zones, especially in the corpus callosum. On the whole, the grey matter is smoky grey while the white matter is speckled with punctiform hæmorrhages. The smaller capillaries become completely blocked with parasitized cells adhering to the endothelium. In areas where there are actual hæmorrhages, macrophage cells abound, but the extravasated cells do not contain parasites. Margulis, Thomson and Seyfarth first described as " malarial granulomata " focal degenerations in the brain substance, the result of hæmorrhages. Granuloma is really an incorrect term, for these lesions somewhat resemble tubercles and are formed by an agglomeration of glial cells around a central focus of degeneration (Fig. 7). They are of some ætiological significance, since they may serve to explain the occasional permanent cerebral phenomena which follow an attack of cerebral malaria.

Three types of cerebral malaria can be distinguished on pathological grounds.

(1) *Massive infection.*—The capillaries are blocked and thrombosed. There are numerous small hæmorrhages with " granulomata " in the subcortical zones. Clinically there is a gradual onset of mental disturbance ending in coma. It is often very difficult to demonstrate parasites in the peripheral blood in these cases.

(2) *Generalized toxæmia.*—This is characterized by fits and convulsions. There are scattered small hæmorrhages. Quinine has no effect and may actually increase toxicity by massive destruction of the parasites.

(3) *Embolism.*—Emboli produce punctiform hæmorrhages, especially in the corpus callosum.

Placenta.—The maternal sinuses may be packed and blocked with subtertian parasites. Infection of the placenta may interfere with the nutrition of the fœtus. It is probable that malaria parasites cannot pass through the undamaged placenta, as spirochætes do. Inoculation with malaria probably occurs at birth (possibly through the umbilical cord, or through a placental tear) when a twelve-day old infant contracts the disease, but there is evidence which suggests that infection may sometimes be acquired *in utero* (p. 49). Abortion may occur, or the child may be born in poor health.

Clinical pathology.—There is no disease which destroys red blood corpuscles so rapidly as malaria except its sequel blackwater fever. To produce symptoms it is estimated that there must be at least one parasite to every 100,000 red blood corpuscles. Reduction of number of red cells cannot be accounted for by the proportion attacked by the parasite. The amount of hæmolysis produced by the mechanical disruption of red cells by the parasites should be easily compensated by the latent physiological hæmogenic reserve, but it is not. According to Brown, hæmozoin (the malarial pigment) may act as a hæmolysin and, when taken up by endothelial cells, destroy red corpuscles and actually cause capillary hæmorrhages. Thus, the reticulo-endothelial system plays a major part in hæmolysis and this possibly accounts for the persistent anæmia which follows a severe attack of malaria. According to modern researches (Malamos) a large proportion of malaria parasites are contained in reticulocytes or the most immature red blood corpuscles. Often after a single attack of subtertian malaria as many as half to one million corpuscles per c.mm. are destroyed (Plate III), with corresponding diminution of hæmoglobin.

Malarial oligocythæmia is accompanied by many changes in the red cells, such as poikilocytosis, anisocytosis, basophilic stippling, and other signs of degeneration of red cells. Basophilic stippling persists for a long period after the disappearance of malaria parasites and may be regarded as evidence of persisting malarial infection. On the whole, in malaria, the corpuscles are larger than normal—particularly those attacked by the benign tertian parasite. Megalocytic anæmia is fairly common. Not infrequently certain small spherical dark-coloured cells are seen, which may be nucleated and are of an embryonic type. There is also sometimes auto-agglutination of the red cells (cold agglutinins).

In acute cases of malaria there is an increase of blood sugar, but in subsequent attacks this rise is not sustained, but is followed by a decrease.

Leucocytes.—Within a few hours of the onset of fever the leucocytes are usually increased during the actual paroxysm. Subsequently there is a distinct fall to 3,000–5,000 per c.mm., the ratio of white corpuscles to red changes from the normal 1 : 500 to perhaps 1 : 900, but in chronic malaria the leucopenia is not so pronounced or so persistent as in kala-azar. In subtertian infection associated with intestinal symptoms there may be a persisting leucocytosis.

Some diagnostic importance has been attributed to the large hyaline or mononuclear cells which play a special rôle in the phagocytosis of malaria parasites and which often contain ingested hæmozoin. D. Thomson has shown that the percentage of these cells, estimated at hourly intervals during the malarial paroxysm, gives a curve which is in inverse ratio to that of the temperature chart. During the rigor and at the height of the fever their numbers are at the lowest ebb, but during the afebrile period an increase takes place, and this persists for weeks after the patient has seemingly recovered. Stephens and Christophers concluded that a mononucleosis of 15 per cent. might be considered diagnostic of malaria, but the figure is not usually above 20 per cent.

Therefore a history of fever, a relative leucopenia, with an increase of the large hyaline mononuclears up to 15 per cent. is strong confirmatory evidence of a malarial infection but, as already stated, a leucocytosis *per se* does not necessarily exclude it.

Phagocytosis.—The hæmozoin (malarial pigment), the detritus of the parasites and the red blood corpuscles are taken up in the blood by the polymorphonuclear and large mononuclear cells. Considerable destruction of red blood corpuscles, both normal and parasitized, takes place in the spleen, where profound pathological changes occur, and this contributes in no small degree to the resulting anæmia. The large number of pigmented macrophage cells (histiocytes) in the splenic sinuses is a striking feature, whilst pigment-containing leucocytes in the peripheral blood afford evidence of malaria infection. The observer must convince himself that this pigment is true hæmozoin and not dust or dirt on the film. The pigment-containing leucocytes are best demonstrated by the thick-drop method. Pigment may also be found within the cells of the cerebrospinal fluid in cerebral malaria. As a rule, in the mononuclear cell it is yellowish-brown, or brownish-black. There is also a shift of the Arneth index to the left and a general diminution of blood platelets.

Other elements in the blood.—There is a fall in the total proteins with a decrease in albumin and an increase of globulins. The increase of the globulin-albumin rate is to be ascribed to the reaction of the reticulo-endothelial system. This is the basis of Henry's reaction (*see* p. 87) which is due to the excess of euglobulin, but which cannot be regarded as specific for malaria. The alkali reserve is diminished as a result of interference with the glycogen metabolism by the liver. In subtertian malaria, during the active stages, the sedimentation rate of the red blood corpuscles is increased.

Polycholia.—Up to a certain point in pathological hæmoglobinuria the liver is capable of dealing with liberated hæmoglobin, so that, when this pigment is set free in the blood, serum secretion and flow of bile (bilirubin) are correspondingly increased. When excessive it gives rise to " bilious vomiting " and " bilious diarrhœa " which are such features of severe subtertian infections and find their highest expression in black-water fever. It is probable also that the yellowness of the skin and scleræ observed in most fevers is due to tinting of the skin with serum bilirubin elaborated by the reticulo-endothelium. Enlargement of the liver is apt to ensue in all four types of malaria, especially in subtertian, and is sometimes accompanied by tenderness.

Blood pigments.—Malaria pigment, or *hæmozoin*, is identical with that formed within the malaria parasites and is to be regarded as an excremental product of the hæmatozoa. Hæmozoin is insoluble even in strong acids, but is altered by potash and dissolved by ammonium sulphide. It is an iron-containing derivative of hæmoglobin primarily split up into globin and hæmatin, and from this latter hæmozoin is derived. It is probably identical with *melanin* and the same as the extravascular product found in bilharziasis and in certain melanotic tumours, but in these conditions it occurs only in cells, never in blood vessels, as in malaria. In the body hæmozoin is most abundant in the splenic vein.

In the organs, especially in the liver, there is usually a deposit of *hæmosiderin* (yellow or brown). This pigment is not characteristic of malaria, but occurs in all diseases in which extensive hæmolysis takes place. Unlike hæmozoin, it is equally insoluble in acids, alkalis and alcohol. Recent researches indicate that under this term two separate components are included. Probably the original pigment after deposition breaks up into free iron and iron-free *hæmofuscin*. These ferrogenous granules are more abundant after an active hæmolysis and can be demonstrated by the potassium ferrocyanide test, in which they show up blue. The hæmozoin is black, whilst the hæmofuscin remains yellow. In a more protacted hæmolysis the yellow pigment is more abundant. Part of the free hæmoglobin which is acted upon by the reticulo-endothelium produces serum bilirubin which gives an indirect Van den Bergh reaction.

PATHOLOGY OF BLACKWATER FEVER

The morbid anatomy and microscopic pathology of blackwater fever present an exaggerated version of that of subtertian malaria.

The *gall-bladder* is filled with dark-green viscid bile. The spleen contains a large amount of hæmozoin, together with evidence of phagocytosis of the red blood-corpuscles by leucocytes and endothelial cells (hæmatophagy).

The *kidneys* are enlarged and congested, and of a peculiar sandalwood or greyish-violet-brown colour, the tubules being blocked with hæmoglobin infarcts, and the cells of the collecting tubules laden with hæmofuscin, while in the capillaries a considerable amount of hæmozoin is found. The blockage of the kidney tubules is attributable, apparently, to two causes: the hyaline or blood-casts, as they are called, are due to the coagulation of highly albuminous hæmoglobin-containing serum, while the cellular are formed by dislodged and degenerate epithelial cells of the urinary tubules which, when impregnated with hæmoglobin, collect in the lumen of the tubules. The appearances are similar to those observed in the kidneys in fatal cases of favism, snake-venom poisoning and incompatible blood transfusion.[1] In more chronic cases the appearances of the kidney are different. Should the patient then die of uræmia, the macroscopic and microscopic appearances of the kidney are those of chronic parenchymatous degeneration.

The *bone-marrow* is brown and fluid.

In the early stages the *blood* shows a great reduction in the number of red blood-corpuscles, but very little other change; the degree of reduction depends upon the extent of the hæmolysis. If it is very extensive, the red blood-corpuscles may fall to 1 million per c.mm. within 24 hours, but in fulminating cases counts of 500,000 have been recorded. At this stage free "shadow" corpuscles can be seen in fresh blood preparations, and it is stated that effete red cells may occasionally be found enclosed in the phagocytes. During recovery the most striking microscopical changes seen are the intense polychromasia and polychromatophilic stippling of the red blood-corpuscles. According to the present teaching, both these changes indicate blood regeneration, and, as evidence of this, nucleated red blood-corpuscles may make their appearance. At the same time, as a rule, a definite increase of the mononuclear cells (about 12 per cent.) can be substantiated; but, save in the absence of malaria parasites, there is no striking feature in which the blood picture differs from that of a serious case of subtertian malaria. In the early stages the serum contains both methæmoglobin and methæmalbumin.

---

[1] On pathological grounds, Maegraith and others do not now think that mechanical blockage of the urinary tubules is sufficiently complete to account for the anuria of blackwater.

SYMPTOMS OF MALARIA

Typical fevers are produced by benign tertian, ovale tertian and quartan fevers.

The characteristic ague is divided into three stages: (1) cold stage, (2) hot stage and (3) sweating stage. One or even all these stages may be absent on occasions, especially when the infection is of long standing, whilst in subtertian fever many symptoms are so bizarre that they may be most misleading, so as to enforce the conviction that in many respects it is quite a different disease.

It is now appreciated that the type of temperature curve, whether *intermittent* or *remittent*, is less significant than it was formerly considered to be. Primary infections of benign tertian may, and indeed often do, produce a remittent temperature chart before finally assuming the classical *intermittent* character. Moreover, two generations of tertian parasites maturing in the blood at different times will produce a quotidian fever, and two generations of quartan will give fever on two successive days—*quartana duplex*—or, conversely, on three successive days—a quotidian fever—*quartana triplex*.

The *incubation* period is usually 10 days; under artificial conditions by mosquito-bite 14 days, but by direct blood inoculation 11 days. When the number of infecting bites is increased, as in subtertian malaria, the incubation period tends to be shorter. In 3·5 per cent. it may be 8 days, but in *latent* cases it may be as long as 30 to 40 weeks. Prolonged incubation periods, as long as one year, have been noted, especially in inoculated malaria. In temperate countries an infection contracted in summer or autumn is often followed by a primary attack in the following spring or summer.

Premonitory stage.—For several days before the actual attack the patient may be conscious of lassitude, a desire to stretch or yawn, aching in the bones, anorexia, sometimes vomiting and a feeling of cold water down the back.

Cold stage.—This usually lasts one to two hours, and is the rigor, or "ague." The feeling of cold is intense and universal. The teeth chatter, the patient shivers from head to foot and wraps himself up in any garment he can lay his hands upon. Vomiting may be most distressing. The features are pinched, the fingers shrivelled and the skin blue like "goose-skin" (cutis anserina). The feeling of cold is purely subjective, because the temperature is rapidly rising. Children usually have convulsive fits.

Hot stage.—The hot stage may last from three to four hours. The shivering abates and gives place to, or alternates with, sensations of great heat. The clothes are thrown off. The face is flushed: pulse full, bounding and usually dicrotic; headache intense; vomiting usual; respiration hurried; skin dry and burning; the thermometer rising to 104°, sometimes 106° F., rarely higher.

Sweating stage.—This usually lasts from two to four hours. The patient breaks out into profuse perspiration with sweat literally running over him in streams, saturating clothes and bedding. With sweating the fever rapidly declines. Headache, thirst and distress give place to a feeling of relief and tranquillity. When it has ceased the patient may feel exhausted, but quite well and able to go about. The body temperature is now subnormal and remains so until the approach of the next paroxysm, one or two days later.

Herpetic eruptions of the lips and nose (fever sores) are common, especially in benign tertian infections, and have been noticed on the ears.

Duration of fever fit.—The total duration of the fever cycle may be from six to ten hours.

Urine and fæces in ague.—During the cold stage the urine is abundant and limpid and micturition frequent; during the hot sweating stages it is scant, cloudy, sometimes albuminous. Urea excretion is increased during the rigor and hot stages, and so is that of the chlorides and sulphates. Phosphates, on the contrary, diminished during the rigor and hot stages, are increased during defervescence. Augmentation in urea excretion commences several hours before the attack, attains its maximum towards the end of the rigor, and decreases during the terminal stages, though still above the normal figure.

A fleeting glycosuria has also been observed from time to time. The urine usually contains urobilinogen and urobilin in excess during the attack, but they decline with the temperature. This is a valuable diagnostic sign, especially in subtertian malaria. The corresponding pigment in the fæces (hydrobilirubin) is increased twenty times the normal amount whilst parasites persist in the blood.

The spleen during ague.—The spleen is enlarged and painful during the rigor, but in early infections not always palpable. At first the enlargement recedes during the interval, but it tends to become chronic if relapses or re-infections are numerous, especially when associated with pronounced cachexia. Spontaneous and fatal rupture may occur in subtertian infections, more usually as a result of direct violence (de Saram and Townsend, 1943). A successful splenectomy does not, as has often been stated, extirpate the malarial infection.

Hennessy and others have recorded that splenic rupture, through causing severe internal hæmorrhage, may produce misleading symptoms which may mimic those of rupture of the bladder by causing urinary irritability and hypogastric pain.

An important lesson for clinicians is that failure to palpate the spleen should not justify omission of microscopic blood examination for malaria parasites. It is estimated that it must be enlarged to twice its normal size in order to be palpable.

Period of the day at which ague commences.—Quite a large proportion of agues " come off " between midnight and noon or in the early afternoon. This time factor may constitute an important point in diagnosis, especially as pyrexial attacks somewhat simulating malarial agues may be caused by liver abscess, tuberculosis, *Bact. coli* infections of the urinary tract and septic conditions, in all of which febrile recurrences are apt to take place during the afternoons or evenings. The fever in meningococcal septicæmia may show a tertian or quartan periodicity difficult to distinguish from malaria.

Atypical agues.—There is an infinite variety of what may be termed "masked malaria," that is to say, malaria without the more easily observable manifestations, especially in subtertian infections, which are apt to become pernicious. There may be a comparatively slight rise of temperature with supra-orbital neuralgia, headache, prostration, vomiting, or gastric oppression and dyspeptic symptoms.

Course of benign tertian and quartan fevers.—Benign tertian ague usually lasts ten hours or less and may be taken as the type of a malarial attack. In some cases the rise of fever is rapid and high, and the temperature may reach 105° to 106° F. within an hour or so; on the other hand, in some cases none of the clinical phenomena are present and the temperature does not rise above 99–100° F. Benign tertian, unless complicated, is not usually fatal; but the persistent and relapsing character makes it a debilitating and tiresome disease. As a general rule, the duration of a simple benign tertian infection before the parasites die out from the peripheral blood is nine months to one year after leaving the endemic area, but exceptions to this rule occur, as clinical relapses, with parasites in the blood, have been recorded as long as three or even four years after the original infection.

The fever in *quartan* malaria is generally smart while it lasts, and is well-defined in its various stages, but it does not produce much systemic disturbance or cachexia. It has often been remarked that, whilst individual attacks of this infection are amenable to quinine and atebrin, the disease is more persistent than tertian or subtertian, so that attacks are apt to occur from time to time over a period of many years and may persist as long as 12 or even 21 years (Shute). It is becoming increasingly realized that quartan parasites may be present in the blood without evoking any special symptoms. The parasites are more resistant to quinine in the sense that they persist in the bloodstream for a week or more while the patient is taking the drug.

Quartan periodicity is the hall-mark of quartan malaria and is hardly ever found in any other disease. Occasionally, quartan fevers are encountered without splenomegaly and apparently without parasites in the blood; their true nature can be ascertained solely by the action of quinine.

Quartan malaria nephrosis.—Although kidney changes are associated with subtertian malaria, nephrosis is commonest in countries where the quartan parasite predominates, as has been noted by Watson (1904), Clarke (1912) in Malaya, Goldie in Palestine, Daniels (1897) and Giglioli in British Guiana and Surbek in Sumatra.

Giglioli, in a complete study, finds that acute *nephritis* is not usually associated with this infection except in the chronic form, and considers that a small proportion of cases are caused by *P. falciparum*. Both sexes are liable to this complication; in childhood the sex distribution is equal, but amongst adults malarial nephritis is commoner in males than in females. He regards albuminuria in a febrile attack as an indication of the commencement of parenchymatous nephritis. The pathology consists of an inflamed kidney which afterwards becomes of the large white variety and eventually degenerates into chronic interstitial nephritis. Goldie, on the other hand, finds that the pathological picture is one of " nephrosis " and is due to the production of malarial toxins continued over a long period. He considers that this may occur in all types of infection, especially the subtertian, but he thinks that the liability in quartan cases is due to insufficient treatment on account of their milder character, and that thus they are more liable to relapse into the chronic stage.

Course of ovale tertian malaria.—This type closely resembles the benign tertian in its periodicity ; but, generally speaking, the attacks are sudden, short and mild, and not accompanied by any grave degree of anæmia or constitutional disturbances. The rigors, in contradistinction to other forms of malaria, are more apt to take place during the evening. Rheumatic-like pains in various parts of the body, especially the lumbar region, are characteristic, and sometimes pain referred to the appendix may suggest appendicitis. Very rarely, more severe types with splenomegaly and anæmia are met, though in these cases a mixed infection with subtertian malaria may be suspected. There is usually no excess of urobilin in the urine, though it is commonly found in other species of malaria infection associated with intense blood destruction.

Course of subtertian or malignant malaria.—From the clinician's viewpoint this is the most important form of malaria. It differs from the others primarily in the greater toxicity and greater variety of symptoms which it may evoke. It may appear in trivial form or rapidly develop into a dramatic and rapidly fatal disease. Some generalizations are permissible.

The rigor stage is relatively less marked, the hot stage and the pyrexial more prolonged, characterized by tendency to an adynamic condition (*see* p. 66), together with vomiting, intestinal irritation, bone pains, anorexia, headache and supraorbital neuralgia. After apparent recovery from fever there is a tendency to recrudescence at shorter intervals than in benign tertian. Subtertian fevers are accompanied by rapid hæmolysis and toxæmia and succeeded by marked cachexia. The parasites sporulate in the internal capillaries and relative blood-stasis ensues, and at any time during the course, *and especially in primary infections*, symptoms of the gravest character may appear. The tendency for successive paroxysms to overlap, or to become *subintrant*, is marked. When intermissions are distinct the crisis is what is called "*a double crisis*." Thus, when the fever has attained its apparent fastigium, there is a drop of one or more degrees of temperature—*a false crisis*—followed by a fresh rise which is then succeeded by a *true crisis*. This peculiar phenomenon has been attributed to the presence of two swarms of parasites in the blood, one of which matures somewhat later than the other ; it occurs ordinarily in one other tropical fever : kala-azar (Chart 4). Such an infection may therefore produce a quotidian typhoid-like temperature chart (Chart 5). Hughes and Bomford (1944) pointed out that in milder clinical forms there is usually a relative bradycardia.

Though this fever may be justly regarded as dangerous to life, yet it is singular that subtertian parasites may exist in the blood for months without seriously interfering with health. Then an explosion may occur, brought about by exposure or fatigue, with dire results, or, it may be, with blackwater fever. Sometimes attention is drawn in other directions—to œdema of legs, diarrhœa, dyspepsia or some other apparently small complaint, quite unconnected with malaria, and these may appear in men returning from West Africa in whom the first symptoms of ill-health may be noted after several weeks' residence in a temperate climate. As

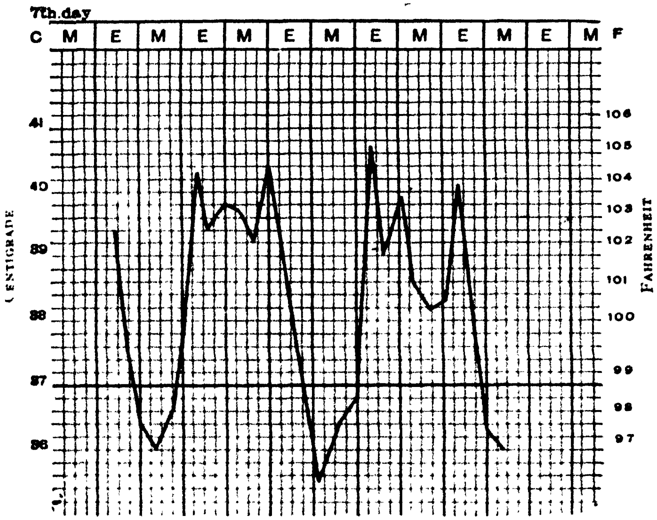


Chart 4.—Subtertian fever (*P. falciparum*).

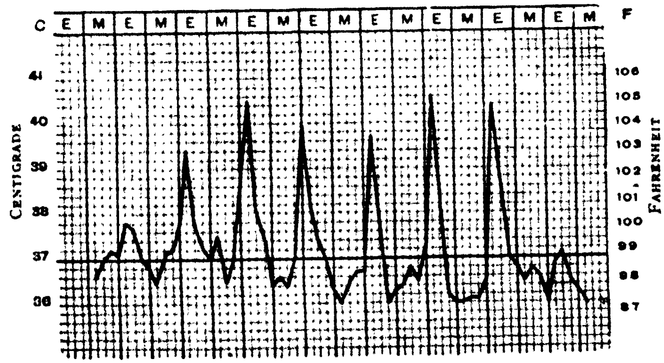


Chart 5.—Quotidian fever (two generations of *P. fa*

this parasite is capable of lying dormant for so long a period it is obviously necessary that the blood of every patient from a malarious country should e examined for subtertian parasites whatever the nature of his complaint. helpful sign is the appearance of urobilinogen in the urine, which sembles sherry in colour.

On the whole, though dangerous to life, the subtertian parasites (in the trophozoite or ring form) are more amenable to quinine and atebrin than are the benign tertian and, moreover, the lifespan of this species in the human body is much shorter, lasting nine months to one year after leaving the endemic area of this disease. The clinical forms which subtertian malaria may assume are many, so that it may simulate many other tropical fevers, even mimicking surgical conditions. Myalgic types, with muscular pains and stiffness, and gastric types, with vomiting and gastro-intestinal symptoms, are frequent in the milder forms. In the acute as well as in the chronic stage spontaneous and fatal rupture of the spleen may take place.

The Editor has seen several cases of this infection producing dramatic symptoms in the absence of demonstrable parasites (after prolonged search) in the peripheral blood.

Bilious remittent.—One type of subtertian fever—bilious remittent—has long been recognized on account of the bilious vomiting, gastric distress, sometimes bilious diarrhœa, sometimes constipation, which accompany the recurring exacerbations. It is further distinguished by the pronounced icteric or, rather, reddish yellow or saffron tint of skin and scleræ—a tint derived, probably, not from absorption of bile as in obstructive jaundice, but from modified hæmoglobin (serum bilirubin) free in the blood or deposited in the skin and sclerotics. These bilious remittents are very common in the more highly malarious districts of Africa, America, the West Indies, India, and, in fact, in all malarious tropical countries. They are not usually dangerous in themselves, but they are apt to result in profound anæmia, and are often the prelude to chronic malarial saturation, bad health and invaliding.

A modification of the bilious remittent—the "typhoid remittent"—is very much more grave, as affecting life, than the simple bilious remittent. In the typhoid remittent, typhoid symptoms—such as low delirium, prostration, dry tongue, swelling of spleen and liver, subsultus tendinum—are superadded to the usual symptoms. Though recovery is the rule, a considerable proportion of such attacks prove fatal.

Some writers class by themselves a set of cases they call "adynamic remittent"—cases which are characterized by restlessness, nervous depression, intense muscular and cardiac debility, profound and rapid blood deterioration, icterus, liability to syncope, occasionally a transient hæmoglobinuria (as was observed in some of the Salonika cases), liability to hæmorrhages, and a marked tendency to local gangrene.

Tuberculosis, syphilis, renal disease, or alcoholism will often be found as factors in determining the adynamic remittent and typhoid remittent types of fever.

Pernicious attacks.—The French neatly designate these *accès pernicieux.* They characterize subtertian infections, and may supervene in apparently mild cases and carry off the patient with horrifying suddenness—as suddenly as an attack of malignant cholera. The wary practitioner is always on the look-out for them, and is always prepared with measures to meet them properly when they threaten. Pernicious attacks are apt to develop in drug addicts (see p. 49). They are classifiable into: (1) *septicæmic* (or toxæmic) type, accounting for about 80 per cent., with numerous parasites in the blood, death taking place from cardiac failure;

(2) *cerebral*, accounting for some 55 per cent., ending usually in coma, in which, compared with other forms, parasites are usually very scanty in the peripheral blood; (3) *algid*, with subnormal temperatures and a clinical syndrome resembling that of shock, accounting for some 14 per cent., and finally (4) *renal*, with œdema and nephritic signs which, though rare, amount to about 1 per cent. of the total.

CEREBRAL FORMS. *Hyperpyrexia.*—There can be little doubt that many of the cases of sudden death from hyperpyrexia and coma usually credited to what has been called "ardent fever" or "heat-apoplexy," are really malarial. If careful inquiry be made into the antecedents, a history of mild intermittent fever will often be elicited; or the patient will be found to have lived in some highly malarious locality.

In the course of what seemed to be an ordinary malarial attack the body-temperature, instead of stopping at 104° or 105° F., may continue to rise and, passing 107°, rapidly mount to 110° (or even, rarely, to 112°). The patient, after a brief state of maniacal or, perhaps, muttering delirium, becomes rapidly unconscious, then comatose, and dies within a few hours, or perhaps within an hour, of the onset of the pernicious symptoms. The skin is hot and burning. Fever sores (*herpes labialis*) are often observed around the lips and mouth. There is an almost distinctive facies. The pulse is rapid and dicrotic, and there may be generalized muscular twitchings. Splenic pain may be prominent. At first there is disorientation with motor aphasia. Incontinence is usually a dangerous sign.

Coma.—Sometimes the patient, without hyperpyrexia (the thermometer perhaps not rising above, or even up to, 104°), may lapse into coma. The coma may pass away with a crisis of sweating; on the other hand, an asthenic condition may set in and death supervene. There is often a paralytic squint, extensor plantar response and Cheyne-Stokes respiration. When subcortical hæmorrhages are present, death usually ensues. There is a marked increase of pressure in the cerebro-spinal fluid, with increase of lymphocytes up to 400 per c.mm., as well as of albumin and globulin. Occasionally, granules of malarial pigment may be found. It is important to note that parasites may be very scanty in the peripheral blood and not infrequently they are absent altogether.

Epileptiform attacks.—There has been some divergence of opinion about the origin of epilepsy following malaria. Mohr thinks that symptoms of meningitis, as the result of damage of brain substance in cerebral malaria, may arise, including epileptiform attacks.

These cerebral attacks depend upon embolism by sporulating subtertian parasites in the capillaries of the various nerve centres: in hyperpyrexia, the thermic centres are involved; in aphasia, Broca's convolution. Monoplegia or hemiplegia may result from implication of various brain areas.

Malarial amblyopia.—In rare instances a comatose pernicious attack ends in blindness. The amblyopia is usually transient, lasting for an hour or two only. On the other hand, it may be persistent; in which case optic neuritis, peripapillary œdema, extravasation of leucocytes, plugging of retinal and choroidal vessels by parasites or pigmented leucocytes, and consequent multiple hæmorrhages, may be found in the fundus. The disc itself is rosy or cherry-pink in which is considered diagnostic. If the hæmorrhages are minute they are discoverable by the microscope only; on the other hand, large retinal hæmorrhages do occasionally occur. There may be blurring of the edges of the discs (Appelbaum and Gelfand), and partial atrophy may follow. These fundus changes differ from those of quinine amblyopia. In the latter, depending on retinal toxic damage, the amblyopia is more persistent; the discs are usually white and the vessels shrunken; central vision is the first to recover (p. 96). (In the modern literature of malaria there are very scant references to the fundus changes. Raynaud in 1892, in a monograph, described the fundus changes in great detail, and de Mussy in 1872 first described retinal hæmorrhages.)

Other cerebral forms.—Besides these hyperpyretic and comatose conditions, other forms of cerebral attack may occur in the course of malarial fevers. Thus, there may be *sudden delirium* ending in coma and, perhaps, death; conditions simulating *cerebro-spinal meningitis*: *delusional insanity*; *dementia*; *acute alcoholism*; various forms of *apoplectic*-like conditions and of *paralysis*, complicated, it may be, with *aphasia*. Seizures of this description, if not fatal, may end in *permanent psychical disturbances*, with a tendency to *suicide*. Temporary debility, or even complete *loss of memory*, may succeed severe cerebral malarial infection.

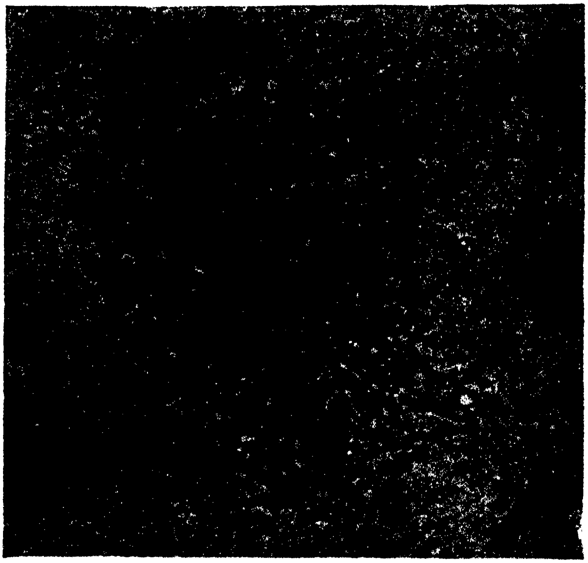


Fig. 6.—Malarial granuloma. Brain section showing plugging of capillaries of cortex and proliferation of glial cells. (*Archiv für Schiffs- und Tropenhygiene.*)

Sequelæ.—Focal degenerations of the brain substance, or malarial granulomata, may ensue as the result of embolism of the cerebral capillaries. These lesions may be responsible for various psychical phenomena following a cerebral attack.

ALGID FORMS.—The algid forms of pernicious attack, as indicated by the name, are characterized by collapse, extreme coldness of the surface of the body, and a tendency to fatal syncope. These symptoms usually co-exist with elevated axillary and rectal temperature.

Gastric form.—This may be associated with, and in a measure be dependent on, acute catarrhal dyspeptic trouble. It is accompanied by severe epigastric distress, tender retracted abdomen, and incessant vomiting. The vomited matter may contain blood.

Choleraic form.—Malarial attacks are sometimes accompanied by choleraic symptoms. The stools suddenly become loose, profuse, and numerous, but generally not so profuse or colourless as the rice-water discharge which pours from the patient in true cholera; they retain a certain amount of biliary colouring, and may be mucoid, or even bloody. As in cholera, the serous drain may lead to cramps in the limbs, loss of voice, pinched features, "washerwoman's fingers," almost entire suppression of urine, and perhaps to fatal collapse. The high axillary temperature, if present; a history, maybe, of recent ague fits; the subsequent rapid cessation of choleraic symptoms on the appearance of the hot and sweating stages; the colour of the stools, and other collateral circumstances, usually suffice for diagnosis, particularly if they are supplemented by microscopical examination of the blood. Although not usual, recurrence of the choleraic symptoms may take place at the next fever period. This dangerous type of malarial fever was noted in Salonika and Palestine during the 1914–18 war, and is said to be prevalent in the Punjab. Without the microscope its true nature may be hard to recognize.

Dysenteric forms.—Another form of pernicious attack is characterized by the sudden appearance of dysenteric symptoms, by severe and recurring hæmatemesis, or by hæmorrhage from the bowel or elsewhere. The possibility of sudden hæmorrhage from the bowel being malarial must therefore be kept in view; particularly if, in what at first sight appears to be ordinary dysentery, the axillary temperature is found abnormally high. Dysenteric forms are explained as due to blocking of the intestinal capillaries by masses of parasitized cells, with consequent necrosis of the mucosa.

Occasionally, in the Editor's experience, it has been possible to demonstrate intracorpuscular subtertian malaria parasites in stained preparations made from the stool. Arafa described sigmoidoscopic appearances in which diffuse hyperæmia and swelling of the mucosa are observed as in bacillary dysentery, and in preparations made from the ulcerated surface he was able to confirm the diagnosis by finding subtertian crescents in the exudate.

Hæmorrhagic forms.—As in purpura, so in these pernicious attacks, hæmorrhages may occur in almost any organ. Purpuric hæmorrhages into the skin may be generally distributed over the body; they may be diagnosed by skin biopsy, and demonstration of the parasites in the capillaries. They are rare, and are commonly associated with better-known phenomena of malaria.

Œdema.—General anasarca with chronic subtertian malaria has been noted in debilitated subjects as, for instance, in war refugees in Greece and in the great Ceylon epidemic of 1934. Wickramasuriya recorded it in 40 per cent. of 857 cases specially investigated in pregnant native women.

It is by no means infrequent in therapeutic malaria (Kopp) and has been regarded as due to marked reduction of the plasma proteins. Œdema sometimes disappears on quinine treatment.

Syncopal form.—In the preceding types of pernicious algid malarial attack the dangerous symptoms mostly show themselves in the rigor stage of the fever. There is another form in which the danger appears to depend on an exaggeration of the symptoms usually hailed as bringing relief and, for the time, freedom from danger. Thus the sweating of the stage of defervescence may be excessive and cause collapse which, if the patient rise up suddenly or make an undue effort, may lead to fatal syncope. Weak and cachectic patients, therefore, should be warned of this possibility. Death from sudden cardiac failure is common in pernicious forms of subtertian malaria, and is due to toxic fatty degeneration of the myocardium (Dudgeon and Clarke).

Acute hæmolytic anæmia.—There is a rapidly developing and progressive anæmia in the fourth or fifth week of a primary subtertian attack, only comparable to that seen in the most advanced stages of pernicious anæmia. These cases are characterized by great pallor of mucous membranes and conjunctivæ, cardiac distress, dyspnœa, hæmic murmurs, and retinal hæmorrhages; the blood-picture by a blood-count of under 1,000,000, extreme leucopenia, a reduction of hæmoglobin to 10 per cent. or under, and macrocytes and megaloblasts in the blood. The pathology of these conditions indicates the hæmolytic nature of the malaria toxin and its action upon the bone-marrow, which shows megaloblastic response. In consequence of the bone-marrow changes and the inhibition of leucocyte production, sufferers from subtertian malaria are especially susceptible to secondary infections.

Rarer clinical forms of subtertian malaria.—Pulmonary forms have been described, with congestion of the pulmonary vessels, bronchitic symptoms or even œdema of the lungs. Rare cases with rapidly developing anasarca and ascites were observed in Macedonia and in Palestine during the 1914–18 war; and, œdematous forms with nephritic signs, such as blood-cells in the urine, have been noted. Disturbances in the vaso-motor mechanism, as in Raynaud's disease, have been recorded, and occasionally gangrene of the toes and fingers, as in a particularly virulent outbreak in Azerbaijan, reported by Shirokorogorov (1935) which was due to thrombosis of venules and changes in the walls of the arterioles.

Orchitis in the course of a malarial attack may be due to agglommeration of parasites in the testes (Mayer and Bastillo).

Practical experience of these suddenly developed pernicious fevers of the tropics teaches the physician never to make light of any malarial attack, particularly if it be of a mild irregular character and imperfectly controlled by quinine, and if small ring forms or crescents be present in the blood; he should be on the alert for any danger signal—mental aberration, restlessness, tremor, peculiarity in behaviour, alteration in knee reflexes, and other indications of grave implication of the nervous system. It further teaches that the subjects of such fevers should be particularly careful to guard against chills and fatigue.

Malaria in pregnancy.—Pernicious symptoms are apt to develop in pregnant women infected with *Plasmodium falciparum*. Cerebral manifestations in late pregnancy arising unexpectedly, without any previous malarial history, may cause serious diagnostic difficulties. The majority are diagnosed as eclampsia. The epileptiform attack in pregnancy is better termed " eclamptic." A lucid interval is very likely to follow intravenous quinine therapy and is apt to lead the inexperienced physician astray.

" Latent " malaria tends to persist through pregnancy, to become active during parturition or lactation. Wickramasuriya, who has adequately surveyed this subject, finds that malaria can modify the course of pregnancy by spontaneous interruption before term ; indeed, malaria *per se* is a far more potent oxytocic than any drug, especially in the ill-nourished who are also suffering from ancylostomiasis. Intra-uterine death of the fœtus is fairly frequent, whilst clinical and pathological evidence points to malaria as a powerful predisposing factor in the toxæmias of pregnancy, such as pre-eclampsia, eclampsia, and " nephritic " toxæmia. In subtertian malaria, albuminuria and œdema of renal origin appear. Hypertension, that most important criterion of pregnancy toxæmia, is often noted. Greater dangers are to be expected when the disease occurs in the later than in the earlier months of pregnancy.

Malaria after operation.—Latent malaria is often brought out by operations and is a definite factor in retarding post-operative recovery ; it may delay wound healing, and show itself only as a tertian, or perhaps a quartan, periodicity with a remittent temperature, parasites being so scanty in the blood as to be easily missed. A Russian author has recently quoted a case in which skin autografts persistently refused to take until the patient was thoroughly treated for malaria. A malarial relapse may take place after any surgical operation, or after parturition, or shock or strain of any description. Surgeons in the tropics would do well to bear these facts constantly in mind.

Malaria in small children.—Malaria, especially subtertian, is a much more severe disease in children than in adults. Benign tertian malaria frequently produces the most alarming symptoms in babies, but it is not necessarily very severe and is easily controlled ; but subtertian malaria is especially likely to assume the cerebral form, and must always be regarded seriously.

Complications.—Subtertian malaria may complicate, or be complicated by, almost any other disease ; a common and very fatal terminal event is pneumonia, either lobar or broncho-pneumonic ; this was noticeable in the influenza epidemic of 1918. Enteric greatly complicates the clinical picture, as do the main forms of dysentery. Pulmonary tuberculosis is very likely to supervene in cachectic cases.

A phenomenon occasionally observed in pernicious attacks, especially in those of an algid type, is flooding of the peripheral blood with vast numbers of parasites, which may be at all stages of development—gametocytes as well as schizonts. The prognosis in such cases is usually bad. On the other hand this may occasionally occur in an attack of average severity.

The chief and most dramatic sequel is undoubtedly blackwater fever.

BLACKWATER FEVER

Synonyms.—Malarial Hæmoglobinuria ; Hæmoglobinuric Fever.

Definition.—The disease consists of an acute hæmolysis of the red blood-corpuscles, which liberates the hæmoglobin into the bloodstream, and in turn produces hæmoglobinuria. It may be considered as an exaggerated form of subtertian malaria. There are certain points of analogy between it and *paroxysmal hæmoglobinuria.*

Geographical distribution.—The disease is undoubtedly most prevalent in Europeans on the West Coast of Africa, from Senegal to the Quanza, but principally on the Congo and in the deltas of the Niger and Gambia rivers. On the East Coast it is also widespread, especially along the Zambesi, the lower Shiré, and the shores of Lake Nyasa. It is far from uncommon on the Upper Niger, in British East Africa (including Tanganyika Territory), in Uganda, in Northern and Southern Rhodesia, in Abyssinia, in the valley of the Upper Nile and in Algeria. It is also common in some parts of Madagascar.

In America it is found, but not so extensively as formerly, over the Southern States of the Union, chiefly Florida, Georgia, Alabama, Mississippi Arkansas, and Texas ; but it has also been prevalent in North Carolina and Virginia. It is found, too, in Central America ; in the Guianas ; on the Upper Amazon and N.E. Brazil : in the plains of Venezuela ; and in the West Indies ; but it has disappeared from the Canal Zone since the introduction of anti-malaria measures.

In Europe it is restricted to Bulgaria, Macedonia, where it is very common, Albania, Greece, Sicily, and Sardinia. A few cases have been recorded in Central Italy.

In Asia it is reported from Palestine, especially the Jordan valley, from Tonquin, the Malay Peninsula, Formosa, from India, particularly Bihar, Assam, Darjeeling, the Terai, Dooars, Meerut, and Amritsar, from Burma and Northern Siam, and from the province of Yunnan, China. It occurs in many of the malarious islands—*e.g.*, Java—of the Eastern Archipelago ; also in New Guinea and the Solomons.

Blackwater fever is not uncommon in England in individuals who have been infected with subtertian malaria in West Africa and other highly malarious countries. It is apt to break out after exposure to cold or over-dosage with alcohol or quinine, as long as eight months after arrival in a temperate climate. Such cases are, as a rule, acute, and the mortality-rate is 50 per cent. or even higher.

Epidemiology.—At times blackwater fever appears to assume an epidemic form. It may not be seen for years in a district, and then numbers of cases may occur within a short time. Very often, as in yellow fever, the magnitude of an " epidemic " may depend on the number of susceptible persons—new arrivals, it may be other than Europeans—within the endemic region ; as, for instance, Bengali clerks in the Punjab, Egyptians in the Sudan, Chinese imported into British Guiana, negroes in Panama, and Central African natives from malaria-free highlands who go to live in the malarial foothills or plains. Thus it broke out among the labourers employed in making the canal through the Isthmus of

Corinth, and attacked the Chinese labourers on the Congo Railway. It is recorded that more than 60 per cent. of the European medical casualties in the German East African force under von Lettow (1914–1918) were due to blackwater fever.

Blackwater is comparatively rare in West African negroes, but now it is as frequent in Arabs and Hindoos as in Europeans. Reyntjens, and also Chesterman, emphasized that, under normal conditions, the negro child, during its first year of life, escapes blackwater though it frequently dies of malaria. When, however, it is protected against the effects of malaria by quininization, it may become susceptible to blackwater.

The occurrence of several cases in the same family may not be pure coincidence, but is probably explained by exposure to a common factor. This has given rise to the term "blackwater-fever houses" in certain districts, especially in Rhodesia, but, when investigated, these prove to be bungalows with exceptionally bad surroundings, and highly malarious. In British Guiana Giglioli has observed the same tendency for blackwater to occur as a family or house disease, and to appear in a given locality at approximately the same period.

Ætiology.—The ætiology of blackwater fever has been the subject of considerable controversy, much of which is now a matter of history. At present it is generally recognized to be the result of repeated attacks of, or continuous infection with, subtertian malaria.

Malaria theory.—It has been observed that, although blackwater fever is co-endemic with malaria in several regions, it is not so in all parts of the world. It has its own peculiar distribution, being absent or very rare in many fever-haunted places. It is common among the Europeans who live in West Africa, and it is also met with in East Africa, though to a lesser extent ; but it is practically unknown among the many thousands of Englishmen who live in some of the fever haunts of India and elsewhere, and it is comparatively frequent in malaria-infected individuals shortly after their arrival in a temperate climate from the tropics. To Deeks and James in Panama must be given the credit of definitely associating the subtertian malaria parasite with blackwater fever and of successfully demonstrating that measures devised for suppressing malaria are singularly efficient in extirpating blackwater fever.

The production by S. P. James of blackwater fever in paralytic subjects artificially inoculated with certain strains of subtertian malaria, and the analogous effects brought about by massive infection of monkeys (*Macaca*) injected with *Plasmodium knowlesi*, have shed a new light on this subject.

In therapeutic malaria no case of blackwater has ever been observed in association with *P. vivax* infection, but solely with *P. falciparum*.

Quinine and other drugs.—One stumbling-block in understanding the true mechanism of blackwater fever is the influence of quinine and other drugs[1] in causing hæmolysis. Quinine in healthy persons, even in poisonous doses, rarely produces manifestations of blackwater fever. Two such cases have been reported in patients with an idiosyncrasy to quinine by Terplan and Javert (1936) and again by Vartan and Discombe (1940). Both these were women who took large doses (76 gr.) of quinine as abortifacients. Fatal hæmoglobinuria resulted, with pathological appearances of true blackwater fever. Methæmoglobin was demonstrated in the urine. Neither patient had ever been exposed to malarial infection. In susceptible normal individuals quinine, in small doses, may produce a transient hæmoglobinuria, as in the instances cited by Manson, Thomson and Macmillan. But true blackwater fever occurs in native races to whom quinine is quite unknown; and, indeed, it was recognized by Hippocrates long before the introduction of cinchona bark. Thus, Connal in Nigeria recorded 24 cases of severe blackwater in negroes who had never taken quinine, and demonstrated from death-rates that regular quinine takers were less liable to a fatal blackwater attack than those who took this drug irregularly.

---

[1] Foy and Kondi have demonstrated that hæmoglobinuria resembling blackwater may be the result

Many observers, especially Thomson in Rhodesia, have shown that certain malaria-infected individuals are specially liable to mild blackwater attacks after even small doses of quinine. Mühlens and Knabe published a case of extraordinary quinine susceptibility in a young patient from West Africa in whom less than gr. 1 quinine-urethane invariably produced blackwater. Fairley and Murgatroyd cited another instance of a double infection with *P. falciparum* and *P. vivax* where a similar susceptibility to quinine was noted, but later, when the malaria infection had disappeared, the drug, even in large doses, had no similar action and there was no evidence of cutaneous susceptibility to quinine.

Blackwater fever has been known to follow the administration to malarial patients of plasmoquine and also of atebrin, in the experience of the Editor and that of Foy and Kondi; but such a sequence is somewhat exceptional. Thus, it becomes evident that any drug of value in the extirpation of subtertian malaria parasites may predispose to blackwater fever, but it is not the only factor.

This statement receives some support from the experiments *in vitro* by Mer, Birnbaum and Kligler (1941), who have shown that laking of red blood corpuscles by bile and bile salts is enhanced by quinine and plasmoquine.

Mechanism of hæmolysis.—Liberation of hæmoglobin—hæmoglobinæmia—takes place, and can readily be demonstrated if the blood-serum is examined the moment the attack occurs; probably by the time hæmoglobin appears in the urine a large proportion of the red blood corpuscles has already been destroyed. The hæmoglobin, some of which has been converted into methæmoglobin, is then excreted by the kidney and forms the typical cylindrical plugs in the renal tubules, which represent coagulation of highly albuminous hæmoglobin-containing exudate. This former explanation of anuria in blackwater is not altogether acceptable to recent workers. Yuile (1942), on physiological grounds, suggested that some primary damage of the epithelium of the convoluted tubules is concerned in elimination of free hæmoglobin, whilst Foy and others (1943), comparing the anuria which may accompany various forms of intravascular hæmolyses, concluded that it results directly from dehydration, diminished blood volume and consequently from diminished glomerular filtration. Hæmolysis is rapidly followed by the appearance of bilirubin and methæmalbumin (*pseudomethæmoglobin*) in the blood-stream, and this accounts for the characteristic saffron-tinted icterus. At the onset of blackwater fever there is usually a sudden contraction of the spleen, and probably hæmolysins are thereby set free into the circulation, but the question still remains to be answered:—what pulls the trigger?

Efforts to demonstrate this factor have hitherto proved in vain. Foy and Kondi (1941) injected the hæmolysing blood of blackwater fever into a recipient who did not develop blackwater or any signs of hæmolysis, although he subsequently developed subtertian malaria.

An important fact has recently been demonstrated by Maegraith, Findlay and Martin (1943). They found that human tissues contain a lytic agent which is inhibited by normal sera. This latter factor is reduced during the hæmolytic crisis of blackwater. As an explanation of this increased hæmolysis it is suggested that the activity of the inhibitory factor has disturbed the balance of the lytic agent and inhibitor to the lytic side.

Modern opinion rather tends to the idea that the essential process represents an anaphylactic reaction from repeated sensitization to the toxins of the subtertian parasite. Thus, Foy and Kondi, during their five years' experience in Macedonia, found a definite relationship between the number of malaria cases in one year and the number of cases of blackwater in an already sensitized population, but no such correlation in an *unsensitized* population. The more the biochemistry of blackwater has been studied the more abundantly evident has it become that it represents an accelerated and exaggerated form of subtertian malaria. Thus, Kingsbury demonstrated that in 90 per cent. of uncomplicated subtertian malarias the serum bilirubin is above the normal figure (0·5 mgm. per cent.) and consequently urobilinogen in pathological amounts is found in the urine.

This excess of bilirubin is excreted by the liver, resulting in an increased flow of bile and bilious vomiting. Normally, in subtertian malaria there is actually hæmoglobinæmia, but this is immediately dealt with by the reticulo-endothelium, but in blackwater hæmolysis is so excessive that the renal threshold for hæmoglobin is broken down and this pigment appears in the urine.

It is important to realize that, even when hæmoglobinuria occurs, most of the hæmoglobin is broken up by the usual mechanism and only a relatively small proportion—17 to 36 per cent.—is excreted in the urine. According to Pearce, before the kidney will excrete hæmoglobin the blood plasma must contain at one time more than 0·06 grm. of free hæmoglobin per kilo. body-weight. This represents about 17 c.c. of laked blood-corpuscles, so that it is possible to have hæmoglobinæmia without hæmoglobinuria. The renal threshold for free hæmoglobin lies between 37 and 102 mgm., per 100 c.c. of plasma ; in amounts greater than this hæmoglobinuria is produced (Fairley). In blackwater there is firstly hæmolysis of the corpuscle and, secondly, conversion of oxyhæmoglobin into methæmoglobin and methæmalbumin. These facts make it improbable that the cause is a true hæmolysin or direct drug effect on the corpuscle. (Methæmoglobin and sulphæmoglobin are examples of *intracorpuscular* conversion of hæmoglobin by drug action.)

Methæmalbumin (formerly known as pseudomethæmoglobin), the new pigment described by Fairley and Bromfield in blackwater, is a brownish pigment resembling methæmoglobin spectroscopically, but is not reduced by Stokes's reagent or ammonium sulphide. Being a non-threshold substance it never appears in the urine. The spectrum has the general appearance of methæmoglobin with the bands shifted. Although it does not reduce with Stokes's reagent this pigment contains a trivalent iron molecule.

The methæmoglobin which has hitherto been described in the plasma of diseases associated with intravascular hæmolysis and hæmoglobinuria is *methæmalbumin*. This error has arisen through failure to differentiate between methæmoglobin and methæmalbumin, though this latter pigment is produced in all conditions of profound hæmolysis. The production of methæmalbumin is apparently brought about by hæmatin (ferric) in plasma by union with serum albumin. The pigment can be synthesized *in vitro* by the addition of alkaline hæmatin (ferric), prepared from pure hæmin, to human and simian plasma at 37° C., but this does not take place with plasma of other animals. Methæmalbumin is therefore a definite chemical compound consisting of a prosthetic group, oxidized hæmatin, and a protein—natural serum albumin.

Schlumm first demonstrated *hæmatin* in human serum, and it gives a spectrum similar to that of methæmoglobin. Hæmatinuria has been found in a series of pathological conditions, such as after potassium chlorate or dinitrobenzol, and in hæmolytic conditions such as pernicious anæmia, paroxysmal hæmoglobinuria, and also malaria.

The hæmolytic agent in blackwater fever may be present in varying quantities in different cases, and at different stages of the same case. Other features are a definite decrease in the plasma bicarbonate and a definite lowering in the alkali reserve in association with urea retention. When clinical evidence of acidosis develops it indicates alkaline medication. This acidosis may appear in the absence of oliguria and ketonuria.

The mechanism of excretion of hæmoglobin products by the kidney has been a matter of controversy. Yuile considered that the presence of granules of hæmoglobin, or its iron-containing breakdown products in the epithelium of convoluted tubules, following injection of hæmoglobin, indicates that this portion of the kidney plays a part in the process of hæmoglobin elimination. Whether this tubular activity is one of excretion or re-absorption, it is agreed that hæmoglobin escapes through the glomerulus, but there is little agreement on the manner in which it does so.

From the clinical aspect estimation of blood urea is important. The amount is invariably raised, especially in cases threatened with suppression of urine. Yorke, Murgatroyd and Owen have demonstrated that the blood urea commonly rises in uncomplicated cases to 65 mgm. per cent. on the fourth day of the disease. (There is a similar rise in severe toxic subtertian malaria.) In one of the Editor's cases of blackwater a figure of 207 mgm. was recorded, with ultimate recovery.

The mechanism of other hæmoglobinurias has been studied. In paroxysmal hæmoglobinuria, if the blood be withdrawn and the serum separated, then cooled to freezing-point, and subsequently warmed to 37° C. with the addition of the patient's erythrocytes, active hæmolysis takes place. This does not occur in blackwater-fever cases. The test by which this fact is brought out is known as Yorke's autolytic reaction.[1]

Donath and Landsteiner have shown that in this disease hæmolysis takes place in the peripheral blood, and that cold is the exciting cause.

The theoretical considerations which underlie this reaction are complicated, and concern the mechanism of immunity, the proportion of immune body and complement. In the serum of paroxysmal hæmoglobinuria the immune body is greatly in excess of the complement, whereas in blackwater fever the reverse obtains.

Dacie, Israëls and Wilkinson have drawn attention to paroxysmal hæmoglobinuria of the Marchiafava type, the chief characteristics of which consist of chronic hæmolytic anæmia, associated with jaundice, and persistent hæmoglobinæmia. Autohæmolysis was demonstrated *in vitro* and shown to be dependent on the *p*H of the system. It has been shown that it is a nocturnal hæmoglobinuria, and that the urine is clear by day. The pigment is found to be methæmoglobin.

Favism in Greece and Sardinia is a syndrome which may be confused with blackwater fever; hæmoglobinuria develops after eating broad beans (*Vicia fava*) (Foy and Kondi). Similar cases have now been described in the United States, Italy, Sicily and Palestine. This is probably an allergic manifestation.

Predisposing causes.—Individuals of all ages and both sexes are liable, but from the facts already put forward it is obvious that blackwater occurs more frequently in European men of mature years who live in the countries where the disease is endemic. At one time race was considered an important factor. In Africa, Europeans, Indians, and Chinese are attacked, while the natives usually enjoy a relative immunity: this is probably not racial but an active immunity acquired by infection with subtertian malaria during childhood, though negroes who live in places which are free from this disease develop blackwater fever as readily as Europeans, if they are exposed to the same conditions. Plehn mentioned serious outbreaks among natives on the Cameroon mountains, those who come to the coast from the interior being especially attacked.

---

[1] (1) Blood placed in incubator at 37° C. at once; no hæmolysis. (2) Serum kept at 0° C. for 5–7 mins., then in incubator for an hour with erythrocytes; hæmolysis. (3) Serum kept at 0° C. for an hour, then in incubator with erythrocytes; little hæmolysis.

Other predisposing causes are debility from previous illness, bad food, hardships of all kinds, dysentery, etc. It has been stated again and again that Europeans are rarely attacked within the first year of residence in a blackwater-fever country, though cases have been reported after so short a residence as three or four months, and exceptional attacks may develop in those who have not previously shown definite symptoms of malaria. Comparable is the dramatic occurrence of blackwater fever in apparently healthy persons who have arrived in England at the expiration of their duty, or on leave. As often as not, the patient gives no previous history of fever while in residence in the tropics. The explanation seems to be that the subtertian infection is lying latent until aroused by the exposure to cold, alcohol, or some other factor.

The disease observes a rough seasonal incidence; it is specially frequent in late summer and autumn in the southern states of America. On the West Coast of Africa it seems to be most prevalent at the close of the rainy season, or in August and September; in Central Africa and Nyasaland, especially in the highlands, a maximal incidence is seen during the wettest months, May to August, when the lowest temperatures are registered. In Southern Rhodesia, where the hot rainy season and the dry cold season are sharply defined, the malarial incidence increases after the rains in April; that of blackwater fever immediately rises also, and is maintained from March to July. During the 1914–18 war, in Salonika and Palestine, cases occurred among the troops especially during the cold winter months.

Symptoms.—It is doubtful whether an incubation period can be described in blackwater fever, but in Central Africa an attack has been noted eight days after exposure to malaria, and Arkwright and Lepper, in their series of cases, state that the maximal interval between the first recognized attack of malaria and the first attack of blackwater fever was ten years (in one case), and the minimal period fifty days.

Some clinicians recognize a clinical condition which, for want of a better term, may be described as a *pre-blackwater state*, indicating a suspicion that blackwater is imminent, and it is wise to be on the look-out for the following clinical signs: The patient is one who has passed through several slight attacks of fever, or at any rate has been infected with the subtertian parasite for several months. The complexion is sallow, the conjunctiva icteric, the liver enlarged, congested and tender, the tongue furred, the spleen generally enlarged, and constipation is the rule. There is usually persistent headache. The urine is dark, owing to the excretion of increased amounts of urobilinogen, and contains a slight amount of albumin. On examining the blood, scanty ring-forms of the parasite may be found, but it is a noteworthy fact that cases of subtertian malaria with high fever and large numbers of parasites in the peripheral blood do not, as a rule, develop blackwater.

The *onset* of blackwater fever is usually sudden. A slight or, more generally, a very severe rigor is followed by intermitting, remitting, or irregular fever with marked bilious symptoms. The pyrexia and rigors do not seem to be the effects of the malaria parasites as much as of a sudden liberation of the products of hæmolysis ; in other words, resembling a hæmoclasic crisis or " protein shock." Earlier or later in the attack, usually during rigor, the patient becomes conscious of aching pain—perhaps severe—in the loins, in the region of the liver and spleen, which are enlarged and palpable, and over the bladder. In exceptional instances these local pains are absent. In response to a somewhat urgent desire he passes water, when he is astonished to see that his urine has become very dark in colour, perhaps malaga-coloured, or possibly almost black. The fever continues, though it is not necessarily very high. Very likely he suffers from epigastric pain and distress, bilious vomiting to an unusual extent and, it may be, bilious diarrhœa ; or he may be constipated. The pain in the loins and the liver-ache continue, and the urine becomes darker and darker. By and by he breaks into a profuse sweat, and the fever gradually subsides. The urine, which hitherto may have been somewhat scanty, now flows freely ; and after passing through various paling shades, from dark brown to sherry red, becomes natural. Usually, and coincidently with the appearance of the dark colour in the urine, or even before this, the skin and scleræ rapidly acquire a deep saffron-yellow tint. This icteric condition persists and even deepens during the progress of the fever, continuing to be a striking feature for several days. When the fever subsides the patient is conscious of a feeling of intense weakness, from which he recovers but slowly. Fever, with or without rigor, may recur next day, or for several days ; or it may cease ; or it may be remittent, or almost continued, in type. The hæmoglobinuria may recur with each rise of temperature, or there may be only one or two outbursts ; it may continue for an hour or two only ; or it may persist off and on for several days or even weeks.

In the more severe form of blackwater there is usually a very great amount of bilious vomiting, of intense epigastric distress, and of severe liver- and loin- ache. The urine may continue copious and very dark, or, continuing hæmoglobinous, it may gradually get more and more scanty, acquiring a gummy consistency, a few drops only being passed at a time. It is considered that the kidneys may excrete up to 36 per cent. of the total hæmoglobin in the blood, though this by no means represents the total amount liberated in many cases. Finally, urinary excretion may be completely suppressed[1].

In severe cases death is the rule. It appears to be brought about in one of three or four ways. The fever may assume the typho-adynamic type ; or sudden cerebral, hyperpyrexial, or algid symptoms may supervene. Hiccough is a fatal sign. In other cases the symptoms may be like those consequent on sudden and profuse hæmorrhage—jactitation, sweating, sighing, syncope. Death may take place from sudden heart-failure after slight exertion, or from exhaustion consequent upon cyclical vomiting, or from sudden hæmorrhage from stomach or bowel. Or it may be that suppression of urine, persisting for several days, terminates, as cases of suppression usually do, in sudden syncope, or convulsions and coma. In very acute cases death may be due to focal necrosis of the liver. More rarely, nephritis may ensue and the patient die from uræmia three or four weeks after all signs of hæmoglobinuria and fever have disappeared, or he may succumb to some superimposed infection, streptococcal, septicæmic, or pneumonic. One attack of blackwater appears to predispose the individual to a second, and second attacks, or more than two, have been noted in Nigeria in about 20 per cent. of cases; according to Stephens, sixteen is the largest number recorded. It is necessary to lay special stress on these points, for when a man has suffered and recovered from two attacks, the third is generally fatal.

---

[1] Maegraith and Findlay (1944) state that suppression of urine does not depend on mechanica lblockage of the urinary tubules, but on peripheral vascular collapse and depression of glomerular filtration.

Blackwater fever is highly dangerous to pregnant women, during parturition or during the puerperium. Particular care should always be taken to guard them from malaria in these circumstances, especially in districts in which the subtertian parasite is most prevalent. Their blood should be frequently examined and they should take prophylactic courses of atebrin from time to time. Thomas and Miller relate a remarkable case of blackwater during pregnancy at the thirtieth week with delivery of a dead fœtus in the middle of the attack. The patient's life was saved by repeated blood and drip transfusions, and the case was still further complicated by a severe attack of *Bact. coli* pyelitis. Foy and Kondi have examined a premature fœtus born of a woman who died of blackwater fever. No trace of methæmoglobin, malaria parasites, or pigment was found in the blood, though the maternal placental spaces were crowded with schizonts of *P. falciparum*.

Sequelæ.—Anæmia and debility are the common sequels of a blackwater-fever attack, but usually, under hygienic conditions, the recovery is astoundingly rapid. A curious sequel is cholelithiasis, owing to the formation of pigmented biliary calculi from inspissation of bile in the gall-bladder. K. D. Fairley originally drew attention to this phenomenon in a case in Australia, and the Editor has since seen two cases in which this was noted three weeks after the cessation of blackwater, and pigmented calculi were demonstrated at operation.

Generally the hæmolysis of blackwater destroys all the parasites circulating in the blood, but occasionally some may escape and produce attacks of fever during convalescence. Exceptionally they may be found in the bloodstream during the blackwater attack and then are apt to coincide with recrudescence of hæmolysis.

The urine.—If the characteristic dark-brown, generally acid, urine of a hæmoglobinuric case be stood for some time in a urine glass, it will separate into two well-marked layers; an upper of a clear, though very dark, port-wine tint, and a lower—perhaps amounting to one-half or one-third of the entire bulk—of a somewhat brownish-grey sediment in which an enormous number of hyaline and hæmoglobin tube-casts are found, together with a large quantity of brownish granular material. Epithelium is also found. Blood-corpuscles may be entirely absent, or few. With the hæmoglobin there is also an escape of the serum albumin of the blood, for the urine, in many cases, turns almost solid on boiling. The precipitated albumin carries down with it, as it subsides, the dissolved and suspended hæmoglobin, leaving a pale-yellow supernatant urine. For some days after the urine has regained a normal appearance it will still contain albumin, though in gradually diminishing amount. Spectroscopic examination gives the characteristic bands of oxyhæmoglobin, as well as those of methæmoglobin. The appearance of oxyhæmoglobin is usual in very severe or fatal cases, methæmoglobin in the less severe or mild, in which the prognosis is more favourable. After the disappearance of the blood-pigments, urobilinogen may be demonstrated in pathologieal amounts and sometimes bilirubin.

Eye complications.—Hæmorrhages into the retina sometimes occur during the course of blackwater, and the Editor has seen one case of altitudinal hemianopia where there was total blindness in the lower half of the visual field.

MORTALITY AND OTHER SEQUELÆ OF MALARIA AND BLACKWATER

Mortality of blackwater.—This varies greatly in the same and in different places, and under the same treatment. Some cases are so mild and transient, amounting, perhaps, to a single emission of hæmoglobinous urine, with little or no fever, that they are unattended with risk ; on the other hand, a practitioner may encounter a run of severe cases which nearly all die. Some old residents in Africa have passed through ten or more attacks with impunity. In Southern Nigeria and in Algeria the case-mortality has been as high as 50 per cent., but, as a general average, it may be put down as about 25 per cent.

Other sequelæ of malaria.—The term *malarial cachexia* is applied to a group of conditions, more or less chronic, believed to be the result of an antecedent attack of severe malarial fever, or of a succession of such attacks, or of prolonged exposure to malarial influences.

The leading symptoms are those of anæmia, characterized by peculiar sallowness of the skin, yellow sclerotics, enlargement of the spleen and, it may be, of the liver. As a rule, the subjects of cachexia are liable to frequent and irregular attacks of fever, though in highly malarious countries it is not unusual to see cases in which fever has never been a feature, or it may have been very mild. In such countries a large proportion of the population have enormously enlarged spleens, causing great protrusion of the abdomen, together with much emaciation and dry, rough skins. It is said that in some intensely malarial countries children are occasionally born with enlarged spleens ; in some instances they are infected through the mother *in utero*, but it is probable that in most cases they become inoculated with parasites immediately after birth.

In the young the general growth of the body is stunted, and puberty retarded. Abortion and sterility are common effects of malarial cachexia in adults.

Cardiac changes in malaria.—Choked capillaries cause injury to endothelium and absorption of malaria toxins with malnutrition of muscular tissue and multiple small necroses. Permanent injury may ensue, and the electrocardiogram may disclose dilatation, extrasystoles and irregular action of the auricles.

The spleen may become so enlarged under repeated attacks of the congestion attending a succession of fever fits, or in consequence of a less active and perhaps feverless hæmolysis, that it may come to weigh many pounds, and be palpable over a large part of the abdomen.

Estimation of malarial prevalence.—The relative absence or prevalence of these enlarged spleens or "ague cakes" in the native population is a rough indication of the malarial risk in any particular district. Wherever they are common the district is malarious, and therefore unhealthy, perhaps to Europeans deadly, and should be looked upon as extremely unfavourable for camping or residential purposes.

Another practical point is that these enlarged spleens are easily ruptured by a blow on the belly; this fact must be remembered in administering even mild corporal punishment to natives of malarious countries. Splenic ruptures are, of course, generally fatal, unless immediately operated on. Occasionally, the spleen may rupture spontaneously, owing to rapid increase in size in the course of an attack of fever; but splenectomy does not necessarily eradicate the malarial infection.

Six cases of ruptured spleen were operated upon in the recent East African campaign. After splenectomy, intravenous transfusion of blood from the peritoneal cavity is an easy and efficacious treatment. The blood is collected, strained through sterile gauze, citrated and given in the usual manner (Erasmus).

Splenic rate or index.—In estimating the amount of malaria in a community the splenic index has been found to be most reliable. Children between the ages of two and ten form the only safe guide (Stephens and Christophers), for among the inhabitants of a very malarious country the adults are more or less immune and their spleens are diminished in proportion. The infantile spleen rate *per cent.* is the basis of the endemic malariousness of a locality, though it is necessary to guard against a tendency to over-estimate its value. Barber, in the Philippines, working with children 5–10 years of age, obtained a splenic index of 13·3 and a parasite index of 11.

It is difficult by any known method to detect changes in the spleen unless they are of some magnitude. Some authorities consider that a spleen must be twice its normal size before it can be felt. The degree of splenic enlargement may be measured with the child standing up or lying down. Considerable differences in the results obtained are given by the two methods, higher values being obtained in the recumbent position. In India and in the tropics generally, where gross degrees of enlargement are commonly encountered, the standing position is nearly always used. The best method is for the child to be drawn gently across the r's knee, the hand being inserted beneath the scanty clothing and pressed the costal margin while the child is told to take a deep breath. The of splenic enlargement is usually classified in finger-breadths below the costal margin. Obviously this method is liable to fallacies. The distance from the costal arch to the pubes is very different in an infant of two years and a child of ten. Christophers devised a method by applying to the actual measurement (costal margin to apex of enlarged spleen) a correction based upon the nipple-umbilicus length of the child.

In the average Indian child of six years of age the four-finger spleen reaches to the level of the umbilicus. In malaria surveys, the following classification is generally adopted :

Spleen-rate greater than 50 per cent. = Hyperendemic.
Spleen-rate 25 per cent. to 50 per cent. = Highly endemic.
Spleen-rate 10 per cent. to 25 per cent. = Moderately endemic.
Spleen-rate less than 10 per cent. = Healthy.

The child spleen-rate gives the measure of endemicity, the average enlargement that of intensity.

Schüffner's method of estimating splenic enlargement has many advocates :

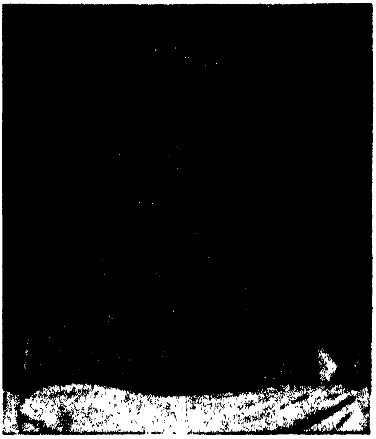


Fig. 7.—Schüffner's method of determining degree of splenic enlargement. (*After Dr. L. W. Hackett.*)

a line is drawn along the left costal arch and a second line parallel to the first is traced from the umbilicus ; these two lines are bisected by a third passing through the apex of the spleen (Fig. 7).

Occasionally an enlarged spleen has to be differentiated from an enlarged left kidney containing a cyst or a hypernephroma ; this has usually a rounded lower pole and a smooth round margin. An area of resonance can be elicited on its anterior surface, caused by the resonant band of the descending colon. The urine contains albumin and casts. Considerable care is sometimes necessary in the accurate palpation of the spleen. This is best done by using the radial aspect of the right index finger with the patient recumbent on his right side and the abdomen relaxed, and the left arm extended (Fig. 8). Most authorities maintain that the greatest degree of splenomegaly occurs in *P. vivax* infections, but that in *P. falciparum* there is a higher proportion of smaller spleens.

Although the chronic fibrous spleen remains quiescent and does not interfere with general health, yet it may occasionally assume an active pathogenic role. Fairley has described a hæmolytic hypochromic anæmia associated with postmalarial splenomegaly of the Banti type in which splenectomy was followed by a hæmolytic megalocytic erythoblastic anæmia.

The parasite-rate or *index* is a simple percentage figure calculated from the number of persons actually showing parasites in the peripheral blood at the time of examination. Figures for children and adults should be kept separate, as the spleen-rate falls with age more rapidly than does the parasite-rate, which shows how many adults of a community are really " healthy carriers."

The *endemic index* includes all those who show either parasites or splenomegaly.

The parasite-rate can be obtained from the study of thick as well as thin films. Curves prepared from splenic and parasite *indices* according to age run parallel to a remarkable degree. The parasite index as a sign of infectivity is more reliable up to five years of age, after which to the age of twenty-five it is on an average 10 per cent. less reliable than the splenic index.

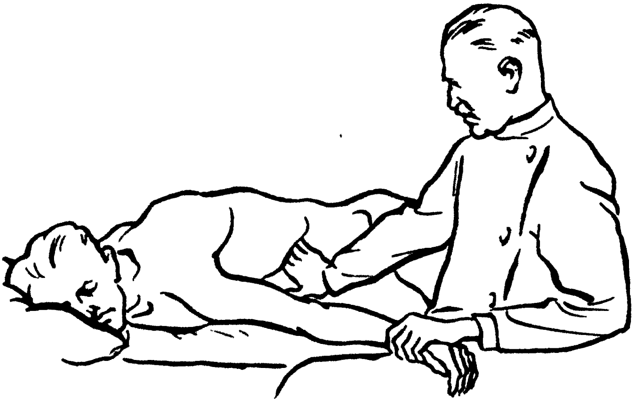


Fig. 8.—Method of spleen palpation. (*After* Munch. Med. Wochenschr.)

Wilson and Clark, in a survey of 1,100 Haitian labourers and 2,007 school-children between 6 and 14 years of age, found that the parasite rate, determined by the thick-film method, was of far greater value in estimating the prevalence of malaria than was the splenic index. Of 11,000 adults 23·5 per cent. had positive blood-films and 3·03 per cent. had palpable spleens : of 2,007 children, 50·52 per cent. had positive blood-films and 3·03 per cent. palpable spleens.

In many areas malaria transmission varies greatly according to the season of the year, mosquitoes usually (but not always) being most prevalent during and after the rains. Spleen and parasite rates observed during heavy transmission periods are likely to be much higher than at other seasons, and, in estimating endemicity, account must be taken of these ctors. In general, a reliable estimate cannot be made, unless rates are over at least one year, and even then that year may be abnormal. e transmission continues throughout the year the rates are more table.

Liver and gall bladder.—Chronic hepatomegaly is a not infrequent sequel of malaria, and hepatic congestion may gradually become more or less permanent. *Siderosis* is produced from chemical changes in the liver undergone by *hæmosiderin*. Together with this there may be chronic engorgement of the gall-bladder, which predisposes to cholecystitis and cholelithiasis. It is small wonder that in this polycholia pigmented calculi are apt to form. For instance Vauthey has recorded 23 cases of biliary colic during an attack, and 71 in which biliary attacks occurred subsequently.

Mental changes.—Loss of memory and mental impairment are frequent sequels of acute subtertian malaria, more especially of the cerebral forms. Schizophrenia has been recorded and also, occasionally, confusional insanity.

Immunity in Malaria

In the course of malarial infection a certain degree of tolerance may develop.

In heavily-infected endemic districts, malaria is specially likely to appear in small children, and of these a proportion die early, while others acquire a degree of immunity through repeated re-infections. It has often been remarked that dark-skinned children with enormous spleens and a rich stock of malaria parasites in their blood run about fever-free, and apparently robust, but they have usually at some time passed through a few years of miserable ill-health. As these children grow up, their immunity becomes stronger and, after twenty years of age, they may remain quite free from clinical signs, and even splenic enlargement may disappear.

It is generally accepted that malaria, like other protozoal diseases, differs from bacterial infections in that the causative parasites do not disappear, but remain in the body, where a balance is established between the resistance of the organisms and the inherent tendency of the parasites to increase. Sergent, Parrot and Donatien have coined the term "*premunition*" to characterize the balance between immunity and re-infection.

Taliaferro and his associates have assigned an important rôle to the reticulo-endothelium and a similar state of affairs has been found by Cannon and Taliaferro in birds infected with avian plasmodia. Ziemann and others have endeavoured to distinguish between immunity to the toxins and that due to the parasites. In the latter case the organisms disappear gradually from the body.

Taliaferro and Mulligan attribute a considerable rôle to the macrophage cells. The reticular cells of the spleen and bone marrow rapidly become converted into the phagocytic phase and may play an essential part in the local defence of these organs.

It is well known that the negro in Africa, although he does get fever, does not get it so frequently or so severely as does the European, although the latter is less exposed to infection. Amongst the Malays Schüffner observed an immunity to malaria parasites, as described by Ziemann. Of the young children, 38 per cent. were parasite carriers, while in the older ones it was as high as 50 per cent. The parasite index in adults was 8–11 per cent., and of those examined, 92 per cent. showed enlargement of the spleen. Christophers (1924) found the same conditions in India. In most districts in the tropics all three classical forms of the malaria parasite occur, and therefore immunity may be produced against all three. In an untreated population, it is found that among children benign tertian parasites disappear most quickly, quartan parasites next and subtertian persist the longest. This is also the case among adults in whom the ring forms of the latter parasite predominate while crescents are very scanty. Thus natural immunity in native populations is the result of natural selection, but each species of malaria parasite appears to be composed of different immunological strains. Thus, natives immune to strains of *P. falciparum* of their own districts may be subject to attacks of subtertian malaria after moving to other areas as a result of infections with new strains.

Sinton, who has given considerable attention to this aspect of immunity, believes that there are two methods of attack upon the malaria parasite and its toxins, viz. (*a*) cellular, and (*b*) humoral, and that these two factors are closely associated and act in combination.

The cellular factor is definitely established in the destruction of malaria parasites by macrophage cells. Primarily, the host reacts to the infection by an increase in the number of these cells ; later, an active *specific* phagocytosis comes into being.

The humoral factors are much less certain; in acquired immunity there is certainly development of specific antibodies and these are probably produced by the macrophage system as the result of stimulation of ingested parasites, acting as a specific antigen. The element concerned may be a lysin, or possibly an opsonin. Antitoxic substances are also probably produced, and there is some evidence to show that a certain degree of passive immunity can be transferred by the injection of serum from an immune subject.

There are undoubtedly individuals who possess an innate immunity against malaria, even when they are residing in heavily-infected districts, but they are exceptional. It is usually asserted that the famous explorer Stanley was one of these. J. G. Thomson estimated that the process of acquiring tolerance to malaria demands continuous exposure for about fifteen years. Experiments by James and others with induced malaria seem to indicate that a certain degree of immunity can be acquired through hyper-infection, but that the immunity is not entirely specific, even for a certain species, but only for a certain strain of parasite. Bagster Wilson has suggested that in non-immunes the subtertian parasite is monomorphic, characterized by minute rings and multiple cell-infection, whilst in immune persons the parasites tend to be larger and polymorphic.

Considerations such as these explain the sudden and severe outbreaks of malaria in endemic districts. No success has so far attended efforts to demonstrate immune bodies in the blood. Sometimes meteorological causes combine to render conditions more favourable for the development of the transmitting anopheles with consequent increase and spread of the disease, as in the Ceylon epidemic of 1934.

Again, mass immigration from malaria-free districts may cause an outbreak of the disease, as in the Panama Canal, and in the many outbreaks during the 1914–18 war. Subsequently the Greeks repatriated rom Asia Minor suffered from serious epidemics with a high mortality in malarious endemic areas in Greece. The widespread malaria epidemic in in 1920 could be traced, for the most part, to migrations of a half- population.

DIAGNOSIS OF THE FOUR CLINICAL VARIETIES OF MALARIA

The recognition of the various forms of malaria parasite in the peripheral blood entails a knowledge of blood examination. For the details of this and of the methods of staining blood the reader is referred to the Appendix, p. 998. Some workers prefer the thick-drop method as offering a more certain chance of discovering the parasites when scanty in the peripheral blood, but it is by no means such a certain method of distinguishing the species.

Effect of quinine, atebrin and other drugs on microscopical diagnosis.—It is of little use to examine the blood for the intracorpuscular forms of the malaria parasite after full doses of quinine or atebrin ; these drugs rapidly bring about the disappearance of this phase of the parasite. The crescent, or gametocyte, of the subtertian parasite alone is unaffected by quinine or atebrin, and in suitable cases may be demonstrated for weeks after the patient is cinchonized ; on the other hand, plasmoquine has a selective action on this stage (*see* p. 99). Changes in the red blood-corpuscles, such as basophilic stippling, are sometimes of assistance, and definite increase of large mononuclear cells above 15 per cent. is suggestive. A reticulocyte crisis occurs 4–7 days after the exhibition of quinine or atebrin.

Complement fixation.—This method of ensuring an accurate diagnosis in chronic cases was originally suggested by Gordon Thomson and considerable attention has been paid to it. As antigen an emulsion of an organ rich in parasites, as well as artificial cultures of plasmodia, have been employed.

Coggeshall (1941) described his special method with an antigen prepared from red cells infected with *Plasmodium knowlesi*. This reaction is uninfluenced by the presence of luetic complement-fixing antibodies in induced therapeutic malaria. The test becomes positive about the second week and persists for some five months. Experimental studies suggest that this test may have considerable merit in *P. vivax* and *P. falciparum* infections. The parasitized red cells are washed free from serum and preserved by freezing and drying. The stored antigen is rehydrated and diluted 1 : 100 in normal saline. The supernatant fluid is used. The tests are carried out as for the standard Wassermann reaction. Dulaney Stratman-Thomas and Warr (1942) found that 81·6 per cent. of malaria sera gave a positive reaction.

Wassermann reaction.—About 28 per cent. of malarial bloods in the acute stages of malaria, when parasites are plentiful in the peripheral blood, give a positive Wassermann reaction ; but this is not so in either the chronic or quiescent stages. This fact has to be borne in mind in excluding syphilis in a malaria-infected subject.

Saunders and Turner (1935) believed that these results are not specific, but that malaria in the acute stage gives rise to anti-complementary reactions. The latest work by Kitchen, Webb and Kupper supports this view. They inoculated 30 persons with *P. vivax* and *P. falciparum* and tested the blood at intervals with the Wassermann and Kahn reactions. They obtained positive tests in every case in which malaria developed clinically ; 72 per cent. of positive reactions appeared during the third and fourth weeks after inoculation of malaria, and these remained positive for more than three weeks in 60 per cent. The highest percentage of positives occurred from fifteen to twenty-one days after the paroxysm.

Try tested 246 malaria patients, the blood being taken when the temperature was normal: 11·78 per cent. gave a positive Wassermann reaction. Of 97 with subtertian malaria, 8·2 per cent.; of 110 with benign tertian, 11·8 per cent.; of 39 with quartan malaria, 20·5 per cent. were positive.

Henry's sero-flocculation test.—From examination of two pigments derived from hæmoglobin—hæmosiderin and hæmozoin—it was considered probable that they would produce in the blood antibodies of diagnostic importance for a flocculation test. Accordingly the ferro-flocculation and melano-flocculation tests were elaborated by employing melanin from ox-eyes. It has, however, become increasingly clear, as has already been suggested (p. 59), that this reaction is non-specific and depends upon an increase of the euglobulin in the serum and diminution of cholesterin serum-albumin (Benhamou and Gille).

Diagnosis by sternal puncture.—Schretzenmayr (1939) claimed that sternal puncture is a simple procedure, and that it should be adopted as a routine diagnostic measure; he found parasites by this method in 19 cases although blood films were negative. Aitken, Rumball and others (1943) have used this method during the present war. They found it valuable in atypical cases, where routine examination of the peripheral blood was negative, especially in subtertian infections. A sternal puncture needle is unnecessary, and a stout truncated lumbar puncture needle can be used. It is inserted vertically through the centre of the sternum at the level of the second intercostal space and pressed firmly through the cortex. Resistance decreases when the marrow is entered. Thick drop preparations can be made, and the fluid contains more parasites than the peripheral blood. Of 294 cases of obscure illness, 256 were diagnosed by blood films, the remaining 38 by sternal puncture. Many of the latter had previously been treated as sandfly fever or neurasthenia.

Diagnosis by splenic puncture. Spleen puncture may occasionally be used as a method of diagnosis, especially in chronic and relapsing cases due to *P. vivax*. In films, malaria pigment, free and endocorpuscular, and remains of malaria parasites may be observed, but Foy and Kondi in Macedonia found this method very disappointing.

Diagnosis of malaria by the therapeutic action of quinine. It is unfortunately true that, where malaria exists, any case of fever is diagnosed as malaria, and the practitioner may be called in only when a considerable amount of quinine has been taken and has failed to achieve the desired result. Unfortunately, too, a good many practitioners are in the habit of relying unduly upon the therapeutic action of this drug, without verifying their diagnosis by microscopic examination.

Diagnosis from clinical signs.—The most important clinical sign is periodicity of the fever, which occurs in its most typical form in the tertian and quartan infections: in the subtertian, however, fever may be most irregular, or there may be no pyrexia at all.

Enlargement of the spleen is a common clinical sign in all forms of malaria. In old-standing infections it may be very large indeed, and occupy the greater part of the abdominal cavity, but in early, and it may be very severe, cases it may not be sensibly enlarged at all, and therefore fails entirely as a clinical guide; usually, however, in the absence of splenic enlargement, splenic *pain* is present during the attack. Moreover, the patient may be suffering from some totally different disease, and the palpable spleen may be the result of a long-standing malaria infection, unconnected with the attack in question.

To the clinician accustomed to many cases, the general appearance of malaria patients, the bright glistening eye, set in rather a dusky orbit, contrasted with the pale and ochreous complexion, combine to create an almost diagnostic appearance. Amber coloured urine due to excessive urobilinuria, especially in subtertian malaria, and even in the absence of parasites in the peripheral blood, may be suggestive.

Diagnosis by the history.—Sudden fever in a previously healthy person who has recently arrived from a malarious country usually turns out to be malaria. The patient will generally give a history of similar attacks while resident abroad, but there are exceptions to this rule, for, occasionally, residents of tropical countries may develop their first attack of malaria shortly after arriving in a cold climate, and this attack, aggravated by the conditions, may run a very severe course; this is especially the case with recent arrivals from the West Coast of Africa, and it is true for both benign tertian and subtertian infections, the parasite lying dormant in the blood-stream, perhaps as long as eight months; in the benign form a year or more.

An actual description of the febrile attack itself may be suggestive. The rapid rise of temperature, the history of the cold, the hot, and the sweating stages, the rapid defervescence of the fever, and the subsequent sense of well-being, are more characteristic of a malarial attack than of any other febrile disease. At times periodicity is a trustworthy enough clinical test. *Tertian and quartan periodicity usually occur only in malarial disease, but have been seen in meningococcal septicæmia.*

Provocative methods of diagnosis.—It has been noted, particularly by Italian observers, that exposure to undue fatigue or cold is apt to bring on an acute attack of malaria fever in latent cases, thus facilitating detection of the parasites in the peripheral blood. It is suggested by some, though to others it may not appear justifiable, that a patient in whom malaria is suspected should be made to climb a high mountain and expose himself to cold at a considerable altitude, in order to provoke an attack.

Other methods have been employed to make the parasites appear in the peripheral blood; e.g. the subcutaneous or intramuscular injection of normal serum or other substances producing protein-shock, sometimes with strychnine, nitroglycerin, iron, ergotin, pituitary extract or adrenalin. Intravenous injection of salvarsan is sometimes followed by a similar result. X-ray applied to the spleen, and ice-packs to the abdomen, are other provocative methods. It is said that the most efficacious measure is the intravenous injection of 2 c.c. of 1 in 1000 adrenalin hydrochloride dissolved in 300 c.c. of normal saline, and that this procedure produces immediate reduction of an enlarged spleen, with the appearance of the parasites in the peripheral blood (*see* Ascoli's method, p. 98).

De Langen and others have shown that the number of parasites in the peripheral blood may be greatly increased after exercise, a process which drives the parasites out of the blood reservoir in the internal viscera where they tend to accumulate.

DIFFERENTIAL DIAGNOSIS OF MALARIA AND OF BLACKWATER FEVER

The differential diagnosis of malaria entails a knowledge of all fevers, both tropical and non-tropical; but there is one point to be borne in mind, for which there seems to exist at present no adequate scientific explanation, namely, that in patients who have suffered for some time from recurrent malarial attacks, the temperature of a subsequently contracted febrile disease, for example measles, may show a periodicity foreign to its usual character.

In hepatic abscess, although the liver is enlarged the spleen is not necessarily so, and the fever occurs generally, though not invariably, in the late afternoon or evening.

In bilious remittent malaria the icteric tinting of the skin is an early feature ; albuminuria is not so common or so marked as in yellow fever.

Without the microscope it is sometimes impossible to differentiate typhoid types of malarial fever from enteric in the early stages.

The following, also, are often mistaken for malarial fever : cerebro-spinal meningitis ; fever of urinary origin (sometimes renal calculus) ; the fever attending the passage of gall-stones, or inflammation of the gall-bladder ; that associated with pyelitis and surgical kidney ; perineal abscess ; lymphangitis, particularly that form associated with elephantiasis and other filarial diseases ; undulant fever ; relapsing fever ; trypanosomiasis ; kala-azar ; the fever associated with tuberculous disease, with ulcerative endocarditis, with some types of pernicious anæmia, with splenic leucocythæmia, with visceral syphilis, with pulmonary carcinoma, with rapidly growing sarcoma, with forms of hysteria, and with many obscure and ill-defined conditions.

Primary atypical pneumonia in its initial stages may resemble a malarial attack, and its recognition gave rise to difficulties in the Middle East campaign. Campbell (1943) described two clinical groups. The first consisted of patients who had both malaria and pneumonia, the second of those admitted with malaria who later developed pneumonia. The routine use of X-rays is indispensable ; it reveals the typical mottling of the lung bases.

Priest, Kilham, Javett and Sacks found that meningococcal septicæmia may produce tertian, or even quartan, periodicity somewhat resembling that of the corresponding forms of malaria. The Editor (1941) diagnosed one such patient, with recurrent attacks of fever, who had been regarded and treated as malaria for nearly one year. Splenic pain may also be present as well as *erythema nodosum*.

Differential diagnosis of special forms of subtertian malaria.—There is a natural tendency for medical men, unacquainted with the clinical forms of subtertian malaria, to diagnose its various symptoms as manifestations of some other disease. Even surgical conditions, such, for example, as appendicitis, intestinal obstruction, or other acute abdominal disorders calling for urgent operative interference, may be suspected. The following statement is based upon actual diagnoses which have been made on clinical grounds alone, without the confirmation of a microscopic examination, but which subsequently proved to be cases of subtertian malaria :

(*a*) *Cerebral forms* of subtertian malaria are apt to be mistaken for heatstroke, mental derangement, hysteria, alcoholism, aphasia, convulsions, epilepsy cerebro-spinal meningitis, or plague.

(*b*) *Abdominal forms* for dysentery, both amœbic and bacillary, cholera, intestinal obstruction, appendicitis, biliary colic, cholecystitis, hæmorrhagic pancreatitis, or liver abscess. Malarial appendicitis can be distinguished on clinical grounds by overcoming the muscular defence by patient palpation, from the subsequent passage of fæces and flatus, the dicrotic, full pulse, the flushed facies, and the rapid fall in temperature after a profuse sweat.

(*c*) *Pulmonary forms*—i.e., malarial pyrexia with pulmonary congestion and myocarditis—for bronchitis, pneumonia, and pleurisy, especially on the left side (due to congestion of spleen), disordered action of the heart or valvular disease.

(*d*) Those with *cutaneous petechiæ* for measles, endocarditis, or purpura.
(*e*) *Febrile* cases with remittent pyrexia for influenza, rheumatic fever, enteric, phlebotomus fever, trench fever, paratyphoid, or relapsing fever.
(*f*) *Icteric* cases for yellow fever, Weil's disease (leptospirosis) or infective hepatitis.
(*g*) *Cachectic* cases for acute nephritis, pernicious anæmia, spleno-medullary leucocythæmia, debility, or pulmonary tuberculosis.
(*h*) *Œdematous forms*, exceptional cases with general anasarca, ascites and polyuria, may be mistaken for beriberi

The lesson to be learned from this statement is the overwhelming importance of blood examination in all cases of fever in malarial countries or in patients who have lived in those countries, no matter how closely the clinical condition simulates other diseases. The finding of malaria parasites, however, does not rule out the co-existence of other diseases, and acute judgment is needed in the evaluation of signs and symptoms.

Differential diagnosis of blackwater fever.—The diseases with which blackwater fever might be confounded are—(1) paroxysmal hæmoglobinuria; (2) bilious remittent malaria; (3) yellow fever; (4) leptospirosis. If it be borne in mind that rigor, hæmoglobinuria and pyrexia are all in evidence at the outset in blackwater fever, and also that blackwater fever is acquired only in certain countries, an error in diagnosis is improbable.

PROGNOSIS OF MALARIA AND BLACKWATER FEVER

As a general rule, **malaria** is a much more serious disease in children than in adults. It is a serious disease in the weakly, especially in those whose constitutions are undermined by any intercurrent disease, such as phthisis or dysentery. It may lead to abortion in pregnant women, and this possibility must always be considered.

A severe attack of **blackwater fever** generally rids the patient of his present malaria infection, but, as the result of this very exhausting illness, his general health suffers for some time afterwards. Patients who have passed through one attack should not be permitted to return, for a year or more, to an endemic centre of the disease. The course of a particular attack can, generally speaking, be judged by the severity of its onset. So far from being protected against future attacks of blackwater fever, the patient appears to be predisposed. Therefore, those who have survived two attacks should not be permitted to return to the tropics; a third often proves fatal.

Apparently mild cases in which fresh paroxysms occur are of grave import. Anuria usually indicates a fatal termination.

TREATMENT OF MALARIA

General management of a case of malaria.—Every case of malaria with fever should be nursed in bed and treated seriously, for severe symptoms may develop at any moment. The room should be darkened to mitigate the photophobia; or a sports shade or eyeshade serves this purpose very well.

Special attention should be paid to clothing; the patient's feet must be kept warm with bed-socks, and after the stage of perspiration the bedclothes should be changed. Attention to the food is also necessary. During the acute stages it is best to give plenty of water and lemonade to drink, while the food itself should be fluid and easily digestible. During the convalescent stages, if the patient has an appetite, full diet should be substituted, and there is no point in denying to patients who are used to it a strictly moderate amount of alcohol; beer and stout in moderation are useful.

For three hundred years it has been almost universally believed that in quinine medical science possessed a unique and specific remedy for this fever—a remedy unrivalled throughout the whole range of medicine in its potency and effects: but during the last twenty years, synthetic specific remedies—plasmoquine and atebrin—which equal quinine in some respects have been produced.

I. QUININE TREATMENT[1]

Quinine hydrochloride is the form which should be used by preference; it may be obtained in tablet form, and taken well crushed up in water: the bitter taste is quickly removed by masticating a piece of bread.

Quinine sulphate pills are to be avoided, as they often pass through the intestinal canal without being absorbed. For this reason *sugar-coated tablets are not recommended for use in the tropics.* Ten grains of the quinine sulphate is rendered soluble in distilled water by 10 minims of acid. sulph. dil., or acid. phosph. dil.

Method of disguising taste of quinine.—In order to disguise the disagreeable taste of quinine, which is so objectionable to some people, syrup of orange or glycerin (1 dr.) may be added. Quinine is rendered less bitter if mixed with milk. A preparation known as *Lacquin* (Cow and Gate Ltd.) is well tolerated and the Editor has had good results from its use, especially in children. This preparation is a powder containing quinine ethyl carbonate, gr. 2½, to one teaspoonful of milk powder, flavoured with vanilla, which may be combined with 10 gr. of aspirin.

Dosage of quinine.—The maximum dose of quinine for an adult European is about 30 gr. (2 grm.) per day. For some infections 20 gr. suffices. With prolonged quinine treatments it is not advisable to give more than 10 gr. a day.

For children, about one-twentieth of the adult dose for each year of age is recommended, so that a child of five years would receive one-quarter of an adult dose. Above fifteen years of age the dose is that of an adult.

Quinine in pregnancy.—Care should be exercised in giving quinine to pregnant women, for undoubtedly, if administered in large doses, it may sometimes cause miscarriage. Pregnancy, however, must not debar the drug altogether; only, in such circumstances, it should be given in the minimum dose likely to be effectual, say 3 gr. repeated every eight hours for two days. *A pregnant woman will run more risk of miscarriage and of detriment to her health from repeated ague fits than from a reasonable dose of quinine.* Indeed, Acton concluded from his pharmacological studies that miscarriage can only be brought about by doses of quinine sufficiently large to poison the patient.

Taken in prophylactic doses it does not interfere with menstruation, conception or pregnancy. It has been shown that atebrin and plasmoquine compounds are well tolerated by pregnant women, and the administration is not attended by undue risks (*see* pp. 100, 102). There is no satisfactory evidence that quinine has any effect on menstruation, although Cook is of the opinion that it increases the amount of flow.

---

[1] Since the occupation by the Japanese of Java, the headquarters of the quinine industry, there has been a great scarcity of this valuable drug. The synthesis of quinine in the laboratory by two American chemists—R. B. Woodward and W. E. Doering—is therefore a discovery of primary importance.

Quinine in the puerperal state.—It is a wise precaution in malarious countries to give a few 5-gr. doses of quinine during labour or soon after. The puerperal state seems to have the effect, as any other shock or physiological strain might, of waking up the slumbering malaria parasite. A dose or two of quinine in these circumstances does no harm, and may, by choking off a threatening fever, avert suffering and anxiety, and even danger.

Excretion of quinine.—Nierenstein's observations show that the excretion of quinine is the same however administered. The drug appears in the urine within fifteen minutes, and altogether one-quarter of the total quantity is passed in this manner, the highest concentration being 7–11 gr. quinine base per litre. Large amounts are also excreted in the fæces.

The Tanret reaction (p. 1005), as demonstrated by Howie and Murray-Lyon (1943), gives important indications in the treatment of subtertian malaria, especially concerning the *absorption* of quinine. Reactions were obtained in acute attacks treated by 30 gr. of oral quinine daily for seven days, and during convalescence after daily suppressive doses of 5 gr. Of 100 patients, 88 showed positive reactions during the attack and made rapid recoveries. Those who gave negative urine reactions all showed unfavourable response to treatment. The majority gave positive reaction between one and five hours after the exhibition of quinine. The reaction may remain negative until intravenous quinine is given, and even this occasionally fails.

Foy and Kondi use Wagner's reagent for the detection of quinine in the blood, while Vedder and Masen have still further improved the colorimetric method by introducing the gum-ghatti and potassium iodide indicator. The Italians make sure that soldiers in the field have taken their dose by coating the quinine pills with methylene blue, which colours the urine green.

Excretion of quinine in milk.—Quinine, even in prophylactic doses, is excreted in the milk of nursing women. To demonstrate this, 10–15 c.c. of milk is drawn off at intervals and added drop by drop to ten times its volume of 96 per cent. alcohol containing 2 per cent. acetic acid, stood for half an hour, shaken and filtered. The amount of quinine in the filtrate is estimated by Tanret's reagent. Excretion commences in fifteen minutes and is completed in one hour.

From time to time it has been suggested that quinine therapy is aided by the addition of alkali. The most widely employed form has been *Sinton's alkaline quinine treatment*, advocated as a standard treatment for malaria in India. The patient is first given, as an aperient, hydrarg. subchloride, gr. 3, followed by 1 oz. of magnesium sulphate dissolved in twice the amount of warm water. Should nausea or vomiting be present, the hydrarg. subchloride can be given in smaller doses with sodium bicarbonate. Two mixtures are given as follows :

(*a*) *Alkaline mixture.*			
Sodium bicarbonate		ʒi	(3·89 grm.)
Sodium citrate		gr.xl	(2·592 grm.)
Aq. dest.	ad	℥i	(28·42 c.c.)
(*b*) *Quinine mixture.*			
Quinine sulphate		gr.x	(0·648 grm.)
Citric acid		gr.xxx	(1·944 grm.)
Magnesium sulphate . .		ʒi	(3·89 grm.)
Aq. dest.	ad	℥i	(28·42 c.c.)

Other forms of quinine.—Euquinine or euchinine, the ethyl carbonate of quinine, has the advantage of being almost tasteless, an important property for children or fanciful patients, and, according to Fletcher, it is as effective as the more familiar salts of quinine. On the other hand, some preparations, such as quinine tannate, are useless, owing to their insolubility.

Quinine alkaloid is almost insoluble in water, but has in consequence less of the bitter taste than the more soluble salts, and appears to be absorbed from the intestinal canal.

Quinidine has an action upon the benign tertian parasite comparable to that of quinine.

Continuous drenching with quinine is of little use in persistent cases. It may be necessary, even in benign malaria, to give a course of intramuscular injections (solvochin) in order to cut short the fever. Therapeutically-induced malaria is extraordinarily amenable to quinine treatment.

Cinchona febrifuge (30 gr. daily) contains all the alkaloids of chinchona bark and gives a cure rate of about 50 per cent. Cinchonine and quinidine in gr. 10 doses, twice daily, have a similar effect in 60 per cent. of benign tertian infections after a course of three weeks.

Fletcher concluded that in doses of 10 gr. twice daily the four alkaloids (quinine, quinidine, cinchonine, and cinchonidine) appeared to be of equal value in controlling malaria, but that quinidine sulphate acts better on quartan parasites than quinine.

There is little to choose between the different crystalline alkaloids of cinchona bark so far as their action on benign and quartan parasites are concerned. In doses of 1 grm. (gr. 15) daily, quinine, quinidine and quinetum are equally efficient in producing a clinical cure in malaria.

Quinetum is a preparation consisting of quinine, cinchonidine and cinchonine in equal parts. This is made by extracting these alkaloids from the bark of *Cinchona succirubra* which contains them all in equal quantities.

Totaquina is standardised to contain not less than 70 per cent. of crystalline alkaloids, of which about 15 per cent. should be quinine. The amorphous alkaloids must not exceed 20 per cent.; mineral matter not more than 5 per cent., and water the same quantity. Two types are prepared:

	Totaquina Type I. Made by extracting the total alkaloids from cinchona bark. (*C. succirubra*)	*Totaquina Type* II. Addition of sufficient alkaloids to residue of quinine manufacture
Quinine	25·23 per cent.	14·79 per cent.
Cinchonine	27·67 „	55·11 „
Cinchonidine	34·13 „	7·10 „
Quinidine	0·0 „	6·21 „
Total crystallizable alkaloids	87·03 „	88·21 „
Amorphous alkaloids	8·86 „	10·47 „
	0·99 „	1·77 „
	0·63 „	2·13 „

(These figures are as given by Chopra.)

Alkaloids in Type I, are chiefly quinine and cinchonidine. In Type II the chief alkaloid is cinchonine and it also contains quinidine and large amounts of amorphous alkaloids.

Results of Totaquina treatment in human malaria.—A single dose of 10 gr. of totaquina Type I produces the same effect in aborting fever and in reducing the parasites as is produced by a single dose of 5 gr. of quinine. With totaquina Type II it is necessary to use a single dose of 20 gr. (1·2 grm.) to produce the same effect as is produced by a single dose of 5 gr. of quinine. Totaquina Type I, when used in ordinary clinical therapeutic doses for curative purposes, e.g., 1·2 grm. (20 gr.) daily for 5–7 days, should give about the same results as quinine in similar doses. It is therefore a good substitute for quinine, and is considerably cheaper to produce.

The term *Cinchona febrifuge* should be strictly reserved for a mixture of all cinchona alkaloids of *C. succirubra* bark which is used for the treatment of malaria in India. The following mixture is prescribed :

Cinchona febrifuge	10 gr.
Citric acid	20 gr.
Magnesium sulphate	30 gr.
Peppermint water	1 ounce

An ounce of this mixture is prescribed three times daily, 2½ hours after meals, for one week. It has been found quite effective, but is apt to produce nausea. It is as effective as quinine in the treatment of malaria and is no more toxic.

The average preparation made in the Government factories in India contains less quinine. It is issued in 3 gr. tablets. The present agitation in the Indian Medical Press is to the effect that this preparation should be used universally as a substitute for quinine. It is said that unwillingness to do so is a matter of prejudice and that it is specially useful in benign tertian malaria on account of its high percentage of quinidine. The average composition of official cinchona febrifuge is :

Quinine	7·4 per cent.	54·65 per cent. of crystallizable alkaloids.
Quinidine . . .	22·83 ,,	
Cinchonine . . .	18·58 ,,	
Cinchonidine . . .	5·84 ,,	
Ash, etc. . . .	45·35 ,,	

Java febrifuqe contains 11·5 per cent. of quinine and a smaller percentage —5 per cent.—of quinidine.

Quinine given in regular dosage is known as anti-relapse treatment. Opinions differ on the best course. Some consider it advisable to keep up the quinine for three months, either by the so-called week-end system—80 gr. on each of two consecutive days—or 10 gr. once a day for six days.

If the spleen is tender, the application of a mustard plaster or a fomentation often gives relief. It is generally held that the absorption of quinine is greatly assisted by the administration of arsenic, and indeed in times of scarcity this drug has been administered in the routine treatment of disease. It is usually

given as liquor arsenicalis, 5 min. three times daily. It may be combined with iron to combat the anæmia, as in the following prescription:

Liq. arsen. acid.	♏iii	(0·178 c.c.)
Ferri sulph.	gr.ii	(0·13 grm.)
Acid. hydrochlor. dil.	♏iii	(0·178 c.c.)
Aq. dest.	ad ℥ss	(14.21 c.c.)

It may be more advantageous, especially during the convalescent stage of the disease, to prescribe iron and arsenic together in pill form, to which strychnine may be added, as in the following:

Ferri hypophos.	gr.ii	(0·13 grm.)
Acid. arsen.	gr.$\frac{1}{50}$	(0.0013 grm.)
Strych. hydrochlor.	gr.$\frac{1}{50}$	(0.0013 grm.)
Exc.	q.s.	

Two or three of the pills are given every night.

Hydroxyethylapocupreine is said by Hegner to be less toxic than quinine and equally effective, whether given by mouth or parenterally.

Esanofele (in pill form) or *Esanofelina* (in solution) has acquired a popular reputation, especially in Italy. Each pill contains:

Quinine bisulphate	gr. 1$\frac{1}{3}$	(0·09 grm.)
Arsenious acid	gr. $\frac{1}{72}$	(0·0009 grm.)
Citrate of iron	gr. $\frac{3}{8}$	(0·027 grm.)
Powdered herbs	gr. $\frac{1}{4}$	(0·0145 grm.)

This is virtually what was known as Baccelli's mixture. The dose for a child under 6 years is two pills a day; from 7–14, four; for an adult, six; as a preventive it is recommended that two pills be taken every day.

Mode of action of quinine.—The effect of quinine on the malaria parasites is not yet clear and it has yet to be proved whether it is direct or indirect.

The fact that malaria parasites, on addition of quinine-saline solution of 1 in 10,000 concentration, are still capable of producing infection after twelve hours is strong evidence against the belief in direct action.

Many investigations have been devoted to the distribution of quinine in the blood and organs of the body; some consider that it is stored in the liver. Giemsa, for instance, thinks that its action is direct and that destruction of the parasites takes place in the endothelium of the vascular capillaries of those organs which accumulate quinine.

Probably, in *complete cure*, both actions come into play, and possibly *direct action* occurs first, as seen in the almost miraculous results of intravenous quinine injection. Furthermore, in ape-malaria it has been shown by Nauck and Malamos that the action of quinine is not interfered with if the main protective organ (*i.e.*, the spleen) is removed.

Toxic effects of quinine.—The milder effects are nausea, tinnitus aurium, dizziness, tremors and palpitations, and are shown by nearly all patients at the beginning of quinine medication. It is even said that their absence indicates that the drug is not being absorbed. Vomiting is occasionally produced and may be controlled by 10–20 min. of adrenalin (1 in 1,000 sol.) in $\frac{1}{2}$ oz. of water.

Idiosyncrasies to the drug are encountered, while some people become [illegible] from long-continued administration; some develop cutaneous eruptions which may vary from a mild erythema to weeping eczema and even exfoliative dermatitis, and general œdema. An indication of this sensitization may be obtained by the scratch test (endermic test). A scratch is made on the flexor surface of the forearm and a drop of 1 in 10 solution of quinine applied. When the test is positive, œdema, with a zone of erythema, results. A saline control should be employed.

Local œdema of the eyelids, as well as of the nasal and oral mucous membranes, has also been observed. Cutaneous hæmorrhages approximating to purpura, with bleeding from the mouth, intestinal or urinary systems, are met, but are rare. Acquired sensibility to quinine is not infrequent, especially if the drug has been given in 15-gr. doses over a long period. After large doses mental confusion and coma may ensue.

Permanent deafness is rare after quinine therapy and occurs only if excessive doses are exhibited.

Quinine amaurosis, due to retinal damage, generally results from gross overdosage with quinine—80–160 gr.—but exceptionally, in those with pronounced idiosyncrasy, temporary blindness may follow even moderate doses. The ophthalmological appearances are œdema of the disc and a cherry red spot in each macula. Injection, intravenously, of 1 c.c. sodium nitrite solution, with paracentesis of cornea, is recommended as an effective treatment. Quinine blindness, according to McGregor (1944), is due to damage to the retinal cells with the production of a "sieve-like" field. The milky appearance is attributed to ischæmia and the cherry-red spot to blockage of the central artery. Total blindness may ensue; usually the arteries become narrow, which may be due to arterial spasm or to a thickening of the intima.

Injection of quinine.—The indications for intramuscular injection are: the inefficiency of oral quinine, its non-absorption owing to severe vomiting or gastritis, the presence of severe, toxic or pernicious symptoms or of large numbers of parasites in the peripheral blood.

The most suitable readily procurable salt for injection is the hydrochloride or, better, the dihydrochloride, which is soluble in its own weight of water.

Pain is caused by the acidity of the dihydrochloride (*p*H. 3·5), and the hydrochloride is better when combined with urethane.

℞	Quinine hydrochlor..		gr. X
	Urethani		gr. V.
	Aq. dest.	ad	2 c.c.
sol. steril.			(*p*H = 6·1)

Solvochin is recommended as an ideal preparation of quinine for injection (25 per cent. solution at *p*H 7·2); 2 c.c. contains 0·5 grm. dissolved in phenyl dimethylpyrazolon. Phenazone is added as a solvent and analgesic. Quinine lactate has been recommended as less irritating than the hydrochloride. Being alkaline, it produces no pain or irritation. In chronic benign tertian malaria 2·2 c.c. is injected twice daily if necessary for four days or longer.

The usual site is the gluteus maximus muscle at a point on a horizontal line through the apex of the great trochanter (Fig. 9). This point, of course, is well above the exit of the deep-lying great sciatic nerve, which may be injured by plunging the needle in a wrong direction. Pain is minimized and absorption aided by massage for some three minutes at the site of injection. The little wound is sealed with collodion. Grey Turner recommends the antero-lateral aspect of the thigh (vastus externus) as the least dangerous site.

A stout, preferably platinum-iridium, needle should be driven well home, deep into the muscles, the skin having been carefully cleansed. The solution must be freshly prepared and boiled, and the syringe and needle thoroughly sterilized.

In children the injection should be given slowly and in dilute solution.

It has been shown that a concentrated solution of quinine is rapidly absorbed from the tissues, and that its action upon the parasites in the circulation is rapid.

Localized necrosis of the muscular fibres of the gluteus is apt to occur after injection of quinine; this is followed by œdema and, it may be, a destruction of the blood-vessels, thus rendering the muscle a suitable culture-ground for tetanus or other organisms. In addition to tetanus and abscess-formation, gas gangrene and general streptococcal septicæmia have been observed. There is no advantage in repeating the injection day after day in approximately the same spot; if this is persisted in, extensive necrosis and hæmorrhage may result (Fig. 10). Injection into or near the great sciatic nerve has resulted in paralysis of the leg.

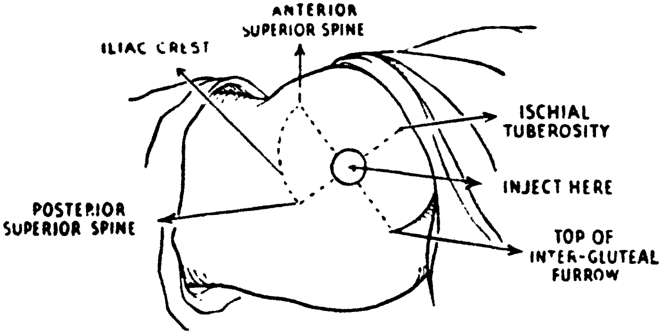


Fig. 9.—Diagram showing the site for quinine injection.
(Burroughs, Wellcome & Co.)

Three or four intramuscular injections of quinine are quite sufficient to tide over the pernicious symptoms of subtertian malaria and to save the patient's life. Continued pyrexia, however, may not necessarily indicate that parasites are still active, but may be due to toxic absorption from quinine injections.

Quinine injections were occasionally followed by fibrous nodules, the size of an almond, at the site of injection. These persist for many years and give rise to a great deal of inconvenience; they may even break down and suppurate many years afterwards. The Editor has seen two such cases in which suppurating sinuses formed at the site of injections given 25–30 years previously. In one case a suppurating granuloma, 2½ inches in diameter, somewhat resembling a sarcoma, was excised from the gluteus muscle. It now appears possible that most of these unpleasant and sometimes dangerous results of intramuscular quinine may be avoided by employing an isotonic solution such as *solvochin*. Wingfield in a series of 500 injections has had no complications. The therapeutic effects have been excellent.

Intravenous injections of quinine.—In pernicious cases of subtertian malaria, in which it is important to obtain a rapid and powerful action, the injection must be intravenous. The dihydrochloride salt of quinine should be used in a dose of 10 gr., dissolved in 10 c.c. of distilled water. In algid or collapsed cases it may be advisable to add saline and glucose

(5 per cent.) injection, in amounts of ½ to 1 pint, though in comatose patients this does not appear to have any distinct advantage. The solution should be boiled in a test-tube before use, drawn up in a sterile syringe and injected into the median basilic vein, rendered prominent by a rubber band. On its introduction into the vein the plunger of the syringe should be slightly withdrawn to let blood enter the barrel. The injection should then be made slowly, after the rubber band has been released, and at least three minutes spent over the operation. One dose of 10 gr. is usually sufficient to stop the fever and cause the disappearance of most of the parasites within eighteen hours, and it is advantageous to follow it up with an intravenous injection of 10 min. of adrenalin (1 in 1,000). If the myocardium is involved, care must be taken, since the amount of toxin liberated by rapid destruction of parasites after intravenous injection may paralyse the cardiac mechanism. It is more advisable, where the myocardium is involved, to give a preliminary intramuscular injection of quinine, and to follow it up six or eight hours later by a smaller intravenous injection (6 gr.). Usually, a considerable fall in the blood-pressure is recorded. If great destruction of red blood-corpuscles has taken place, blood transfusion of 800–500 c.c. is indicated. (*See also* p. 105.) American authorities have recently advocated large doses of nicotinic acid as a vaso-dilator in these cases.

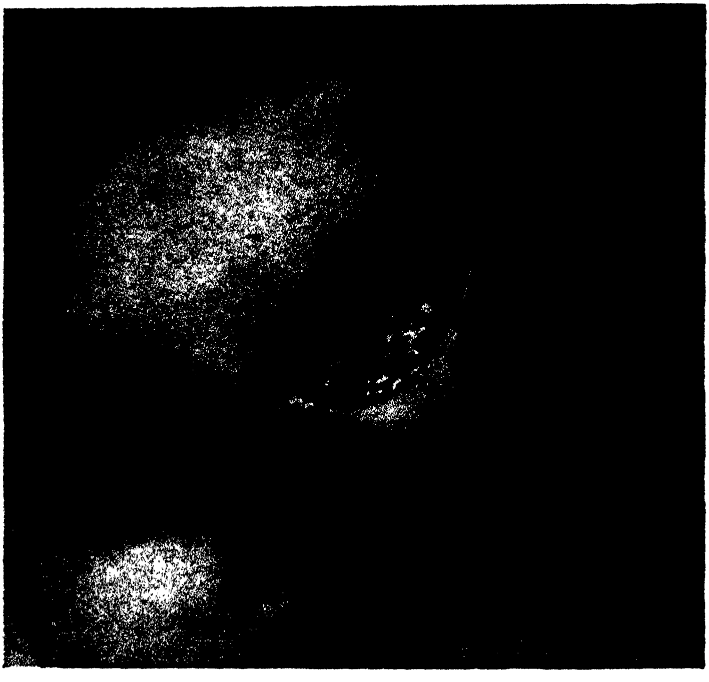


Fig. 10.—Quinine abscess of buttock, developing ten weeks after last quinine injection.

The Ascoli treatment.—In Italy a good many papers have appeared on this method since it was first introduced by Dominici in 1931. Ascoli's method consists in the intravenous injection of adrenalin, $\frac{1}{100}$, $\frac{1}{50}$ and $\frac{1}{30}$ mgm., in increasing doses up to $\frac{1}{10}$ mgm. Usually, about twenty daily injections are needed. This method results in reduction of the size of the spleen, decrease of anæmia, increase of body-weight and improvement in general health. It is also said to increase the efficiency of subsequent quinine treatment, especially in those resistant to this drug (Pizzillo).

Milletari (1938), in 70 cases of malaria, confirmed the great value of this treatment, not only in its remarkable effect upon the splenomegaly, but also in the great improvement in general condition. He believes that it increases resistance to the malaria parasite, and this was confirmed by D. Bell in Kenya.

Stephenson (1940) found this method efficacious in the Sudan in cases with enormous malarial splenomegaly. Treatment was continued for 29 days. Enlargements of the spleen from other causes were uninfluenced. Other observers, such as Casini and Marotta, have reported unfavourably.

II. SYNTHETIC ANTI-MALARIA PREPARATIONS

Plasmoquine (pamaquin or præquine, British; rhodoquine, French) (6-methoxy-8-N (4′-diethylamino-1′-methylbutyl) aminoquinoline) is a derivative of methylene blue (*see* Table, p. 820). When given in a dosage of 0·04 grm. daily for five consecutive days, it has an action on the benign tertian and the quartan parasites, which disappear from the blood with a rapidity equal to that seen with quinine; on the subtertian trophozoites its action is not so satisfactory.

The maximum therapeutic dosage of *plasmoquine simplex* is:

0–6 months	0·0025 grm. three times daily
6 months to 2 years	0·005 „ „ „ „
2 – 4 years	0·0075 „ „ „ „
4 – 8 „	0·01 „ „ „ „
8 –10 „	0·015 „ „ „ „
10–15 „	0·02 „ „ „ „

The drug is usually dispensed as tablets of 0·01-0·02 grm. each. The maximum dosage is 0·06 grm. daily.

In all four malaria infections, gametocytes are destroyed before schizonts, so that crescents of the subtertian parasite (which may persist for weeks in the circulation on quinine therapy) can no longer be found after four days' full dosage with plasmoquine. The spleen is rapidly reduced in size. Especially in heavy subtertian infections, cyanosis, due to intracorpuscular conversion of hæmoglobin into methæmoglobin, is sometimes noted and, in a few instances, has been followed by methæmoglobinuria (as in the fatal case reported by Blackie); abdominal pains are often produced, especially acute spasm in the left hypochondrium, which may be connected with contraction of the spleen. De Langen and Storm showed that both *plasmoquine* and *atebrin* in excessive doses cause circulatory disturbances, manifested in a reduction in the blood-pressure; and, when injected *intravenously*, 1 c.c. of 0·1 per cent. plasmoquine and 1 c.c. of a 2 per cent. solution of atebrin cause a fall of both systolic and diastolic pressures. In fatal cases of plasmoquine poisoning acute hæmorrhagic nephritis and toxic necrosis of the liver occur.

Whether plasmoquine is more apt than quinine to precipitate *blackwater fever* is still undecided and is difficult to determine on account of its tendency to produce toxic methæmoglobinuria. The test for determining plasmoquine in the blood and tissues is that of Nandi and Dikshit (sensitive in a strength of one in a million). Applied to the urine it is unsatisfactory. The method is an application of Folin's phenol reagent, which is added to an aqueous solution of plasmoquine and rendered strongly alkaline by the addition of sodium bicarbonate. A blue colour develops, slowly reaching its maximum in thirty minutes, and can be detected in a dilution of 1 in 200,000 by the Duboscq colorimeter and of 1 in 1,000,000 by means of a spectro-photometer.

Parenteral injections of plasmoquine are not recommended.

In the present war plasmoquine has been found to have a limited effect on malaria.

Certuna (dialkylamino-oxyquinolamino-butane) has been reported by Kikuth to possess a strong gametocidal action comparable with that of plasmoquine. The action upon gametocytes and sporozoites is the same as that of plasmoquine, but its toxicity is less. Sioli gave 0·07 grm. three times daily for seven days with good results, and Mühlens advised doses of 0·01 to 0·02 grm. thrice daily for 3–5 days. It can be given safely combined with atebrin. A similar drug was synthesized by Schulemann under the name of "cilional." Missiroli and Mosna gave 2 cgm. daily for six days, but stated that when combined with quinine or atebrin it provided a complete antimalarial remedy, its action on the gametes of *P. falciparum* being equal to that of plasmoquine.

COMBINATIONS OF QUININE AND PLASMOQUINE

Plasmoquine-compound.—The toxic effects of plasmoquine appear to be counteracted by combining it with small quantities of quinine. This combination is now known as plasmoquine-compound and is put up in tablet form, each containing 0·01 grm. of plasmoquine and 0·125 grm. of quinine. Plasmoquine-compound is comparatively tasteless and appears to be well tolerated by children. It is as effective as quinine in treating benign tertian malaria and in preventing relapses. In the subtertian form the schizonts do not disappear from the blood with such rapidity as with quinine, but the same specific action on gametocytes is observed. The Editor showed that subtertian crescents disintegrate and disappear from the circulation after 0·08 grm (1¼ gr.) plasmoquine and 1 grm. quinine, but with quinine alone, crescents may remain visible in the bloodstream for twenty-eight days and after 56 grm. The following course of treatment can be carried out in benign tertian and quartan malaria.

For an adult :

(1) 7 days. 2 tablets plasmoquine-compound twice daily.
(2) 4 ,, interval
7 ,, 2 ,, ,, ,, twice ,,
(3) 4 ,, interval
7 ,, 2 ,, ,, ,, twice ,,
(4) 4 ,, interval
7 ,, 2 ,, ,, ,, twice ,,
(5) 4 ,, interval
7 ,, 1 tablet ,, ,, twice ,,

Children between 4 and 5 years : 1 tablet plasmoquine-compound twice daily.

Children between 5 and 10 years : 1 tablet plasmoquine-compound thrice daily.

Toxic symptoms may to some extent be eliminated by the exhibition of glucose, 1 fl. oz. daily.

It has been shown by the Editor that plasmoquine-compound in therapeutic doses (0·04 grm. plasmoquine daily) is a safe drug to use in benign tertian, quartan and subtertian malaria, both during pregnancy and in the puerperium.

Quinoplasmine (Chinoplasmin). Plasmoquine : quinine 1 : 30.—This is a combination of plasmoquine with a larger proportion of quinine than in plasmoquine-compound. The tablet contains 0·01 grm. plasmoquine and 0·3 grm. (4½ gr.) quinine. The dose is three tablets daily for adults and represents a otal dosage of ⅓ grain of plasmoquine and 15 grains of quinine. Kliger, in Palestine, used this preparation (five days in each month in the doses stated) for reducing the parasite-rate in a malarious community; apparently no toxic symptoms were noted.

This is much the same method and dosage as was tested out by Manifold in India in 1930 when 3,187 British and Indian soldiers were given a three weeks' course of plasmoquine and quinine—plasmoquine 0·02 grm. (gr. ⅓) together with 10 gr. of quinine—every morning and evening. In subtertian malaria this course was followed by 0·04 grm. plasmoquine daily for five days, but the majority were benign tertian. It was concluded that this course was most efficacious in preventing relapses, and an advance on ordinary quinine treatment. It was possible, however, that in 0·1 per cent. of cases an attack of blackwater may have been precipitated.

III. Atebrin[1]

Atebrin (mepacrine hydrochloride; mepacrine methanesulphonate, British; quinacrine, French; acriquine, Russian) (dihydrochloride of 2-methoxy-6-chloro-9 (4′-diethylamino-1′-methylbutyl) aminoacridine) is a yellow powder which dissolves in water at 40° C in 7 per cent. solution.

Kikuth proved that atebrin exerts specific action on the schizonts of all the malaria parasites, but has no direct action upon gametocytes, especially subtertian. It attacks ring forms first, then developmental forms and, finally, if the atebrin is given for long enough, gametocytes disappear; but, as shown by the Editor and Walters, exflagellation is not at any time affected, as it is with plasmoquine. Undoubtedly the most beneficial effects are seen in the treatment of heavy infections of subtertian malaria. There is also evidence that it is the safest drug when blackwater fever is threatened, for it does not possess the hæmolytic properties of quinine.

Atebrin is accumulated in the body, as shown by the staining of the skin. It also accumulates in the liver, spleen and reticulo-endothelial system. Complete elimination is slow, and in some cases takes a month.

A further advantage over other malarial remedies is its comparative freedom from toxic symptoms, but these have been noted in some people with an idiosyncrasy, and it may cause acute abdominal pain, sometimes so severe as to suggest gastric ulcer. Sometimes, also, it produces a yellow discoloration, or staining, of the skin, which may be mistaken for jaundice. Atebrin pigmentation never occurs before the third day, while constipation or intercurrent infections modify its intensity and duration; sometimes it may persist as long as three months. Recently the tablets have been coated with lacquer, which appears to some extent to obviate this drawback. In differentiation from true jaundice, acholuric jaundice and pernicious anæmia, it should be remembered that the scleræ are not usually discoloured by atebrin. Carotinæmia is easily differentiated.

Attention has recently been drawn to the fact that, in some individuals, atebrin in large doses acts as a cerebral excitant, and the Editor has seen a few patients who have experienced feelings of undue excitement. Green and Hoops noted the phenomenon in Malays, and Neave Kingsbury reported some twelve cases of psychosis in Tamils, Malays, Chinese and Sinhalese. Some exhibited mild or transient psychoses, while others presented more serious symptoms necessitating special mental care. Kingsbury suggested that liberation of malarial toxins, due to rapid destruction of parasites, has an adverse effect upon the cortical centres.

Blackwater fever may ensue after a course of atebrin, as noted by several observers. The Editor has seen one such case; but the general impression prevails that it is less frequent than after quinine.

---

[1] The generally-accepted British name is mepacrine (p. 821).

The amount of atebrin in the blood and urine can be estimated by microchemical methods (*see* Appendix, p. 1006). It is now realized that its value, both in treatment and causal prophylaxis, depends upon absorption, so that the estimation of atebrin blood levels is important and is now the subject of intensive research.

Atebrin is dispensed in tablets each containing 0·1 grm., and is usually given three times a day *on a full stomach.* The daily dose therefore is 0·3 grm (4½ gr.). In West and East Africa several observers consider that larger doses are well tolerated and more effective so that 0·6 and even 0·9 grm. have been given for the first and sometimes the second day, without ill effects as long as plenty of fluid, such as hot tea, is taken at the same time. Until recently it was considered that a five-day course of treatment sufficed to cure an average case of subtertian malaria, but it is now realized that seven days may be necessary with a total of 2 grm. It is much safer to repeat the course, for a similar length of time, after an interval of a week. Several authorities during the present war consider that intense pigmentation of the skin is really essential to produce rapid cure. It is important that the tablets should be swallowed with a drink of milk or water, as the taste, when chewed, is intensely bitter. Atebrin treatment is less satisfactory in benign tertian and quartan than in subtertian cases.

Atebrin treatment can with advantage be combined with 5–10 gr. of quinine hydrochloride daily. This method, which has been employed by the Editor, has been confirmed by Ciuca and his colleagues (1938), especially in severe subtertian infections.

Shrinkage of the spleen takes place as rapidly as in quinine- or plasmoquine-treated cases.

The drug is well borne in relatively large doses by pregnant women, which is important. The most valuable property of atebrin is its high power of preventing relapses. Green in 1932, treated 21 cases without relapse, while in a similar period there were, 13 relapses among 34 controls treated with quinine. James and Nicol treated 15 cases of therapeutic (subtertian) malaria with 0·3 grm. daily for five days, and in only one did it fail to effect a permanent cure; four of these were chronic relapsing cases which had previously been subjected to several courses of quinine treatment. Hoops reported that in Singapore atebrin gave satisfactory results both in Europeans and Asiatics; a sense of well-being is experienced which is not noted with quinine or plasmoquine. The relapse rate, over a period of six months, in 803 cases made up of approximately equal numbers of benign tertian and subtertian infections, was reduced with atebrin treatment to 8·4 per cent. On the long course of quinine treatment it was 23 per cent., and with combined quinine and plasmoquine 20 per cent.

Atebrin is probably equal in therapeutic action to quinine, but it is slower, especially in subtertian malaria; it gradually influences the fever, and destroys the parasites. Nausea and headache disappear. Children tolerate atebrin well, and the following doses are recommended:

Up to 1 year . . .	0·05	grm. (i.e., half a tablet)	daily	dose
From 1–4 years . . .	0·1	„	„	„
„ 5–8 „ . . .	0·2	„	„	„
Over 8 „ . . .	0·3	„	„	„

For children atebrin is best given in milk, or the tablet can be conveniently hidden in raisins.

Intramuscular injections of atebrin are less painful than those of quinine. Two injections with an interval of twenty-four hours are recommended. The drug in a soluble form (*atebrin musonate*) is supplied in sealed ampoules containing either 0·1 or 0·3 grm., and the contents are dissolved in 3 or 9 c.c. of water respectively. In very severe subtertian infections, however, its action is not nearly so certain as intramuscular quinine and, in the Editor's experience, it should not be relied upon in very severe cases.[1]

With this strength (0·3 grm. in 9 c.c.) the dose is

From 6 months to 2 years	1 c.c.
,, 2- 4 years	2 c.c.
,, 4- 6 ,,	3 c.c.
,, 6-10 ,,	4 c.c.
,, 10-12 ,,	5 c.c.
,, 12-15 ,,	6 c.c.
,, 15-18 ,,	7 c.c.

Field and Niven and Guest, comparing the action of atebrin musonate (intramuscularly and intravenously) in doses of 0·3 grm. on two successive days, found that parasites disappear from the blood and temperatures fall to normal as quickly as with quinine. The contents of each ampoule should be diluted in 3 c.c. of water for intramuscular injection and in 9 c.c. for intravenous. Though effects may be rapid, however, cure is not permanent. Usually the local effects of intramuscular injection are transient, but sterile abscesses have resulted. This method is contra-indicated in cases with severe *anæmia.*

Excretion of atebrin is rapid at first, and this may considerably influence the concentration in the blood. Traces have been found in the urine within ten minutes. Excretion usually takes place in the urine (to which it imparts a bright yellow colour) and in the fæces. It may be prolonged for several weeks, the average period being 26 days. Urticaria has been seen in cases hypersensitive to atebrin.

Intravenous injections of 0·2 grm. atebrin musonate have been given in cerebral malaria, but are not nearly so efficacious as quinine.

The *simultaneous* exhibition of atebrin and plasmoquine is *not to be recommended,* as it may cause alarming symptoms. On the other hand, an atebrin course followed by plasmoquine-compound is a rational procedure and has received commendation, especially when gametocytes are numerous. The following method of application is recommended :

> Seven days' atebrin treatment followed by the administration three times daily, for three to five days, of 0·01 grm. plasmoquine simplex, or one tablet of quinoplasmine, three times daily.

Malaria parasites undergo certain degenerative changes after the exhibition of both atebrin and plasmoquine. The former causes an aggregation of the pigment of the parasite within two hours, and sometimes pigment-free gametocytes (crescents) are produced (Sinton) ; the latter appears to act directly on the chromatin.

Reports on the success of this combined treatment come mostly from Malaya. In Central America Connor reported that relapses were 2–5 per cent. as against 25–30 per cent. after quinine treatment.

---

[1] American authorities disapprove of intravenous mepacrine. Hawking found that the effects of mepacrine dihydrochloride and methane sulphonate by intramuscular injection are similar : both produce necrosis. Subcutaneous injection is contra-indicated as it produces extensive necrosis.

Sulphonamides.—Both sulphanilamide and sulphanyl-sulphanilate have been found effective in ape-malaria, *P. knowlesi*, especially by intraperitoneal injection. Sulphathiazole in doses of 6 grm. daily, spaced in doses at intervals of four hours, for four days, extirpates the benign tertian parasite as effectively as it does *P. knowlesi* (Pakenham-Walsh and Rennie). Research on the more recent sulphonamides is now being actively prosecuted.

Salvarsan and derivatives appear to have some influence upon *P. vivax*, but little or none on other species. Salvarsan has been employed at weekly intervals as an adjuvant to quinine, and in some cases it appears to act as a general tonic, especially when there is a superadded syphilitic infection.

Stovarsol in 4 gr. tablets, twice daily for ten days, has been credited with some curative effect, especially in benign tertian infections.

Mapharsen (meta-amino-parahydroxy phenylarsine oxide) intravenously may cut short a malarial attack in doses of 0·04 to 0·06 grm., according to the body-weight. Goldman claims that in 90 per cent. a single injection suffices, and that it is of special value in cutting short therapeutic malaria.

Thiobismol (sodium bismuth thioglycollate), injected intramuscularly in 0·2 grm. doses, exerts a definite effect upon therapeutic benign tertian infections (*P. vivax*) and produces remissions of 48 hours (p. 52).

Quinine treatment of benign tertian or quartan attacks.—During a paroxysm of ordinary benign tertian fever it is better, before giving quinine, to wait until the rigor and hot stages are over and the patient is beginning to perspire, but in subtertian malaria it is wise to begin treatment as soon as diagnosis is established. When the skin is moist and the temperature begins to fall, the earlier the drug is commenced the better: 10 gr., preferably in solution, should be administered at the commencement of sweating, and thereafter 10 gr. three times a day after meals for the next three days, though there appears to be some advantage in giving it, whenever possible, in smaller doses at more frequent intervals —6 doses of 5 gr. each. If the patient is constipated, a saline purge should be administered before the quinine. The quinine may not always prevent the next succeeding fit, but it nearly always diminishes its severity; in ninety-nine cases out of a hundred the second following attack does not develop.[1] At the same time, with a view to preventing recurrence of fever, the patient is directed to take, once a week, a mild saline, e.g., sulphate of soda in the morning, and three 5-gr. doses of quinine during the day, or 15 gr. in one dose. After the first week, iron and arsenic are given, in pill or tabloid, such as:

Ferri hypophos.	gr. ii	(0·13 grm.)
Quin. sulph.	gr. i	(0·065 grm.)
Acid. arsen.	gr. $\frac{1}{50}$	(0·0013 grm.)
Strych. sulph.	gr. $\frac{1}{50}$	(0·0013 grm.)

Two pills to be taken at night for a fortnight.

Anti-relapse treatment with plasmoquine-compound may be then given by those who prefer this method.

Treatment of subtertian malaria.—Mild cases of malaria of the subtertian type, due to *P. falciparum*, may be treated on the same lines as the benign forms, with quinine combined with atebrin (*see* p. 102).

---

[1] In resistant cases, which have been common during the war, there should be no hesitation in injecting quinine intramuscularly (*see* p. 97).

Rest is a most important factor. It is undoubtedly true that the malignancy of many cases of subtertian malaria observed in military service is due, to a great extent, to the exigencies of war.

The sooner after infection a case of subtertian malaria is treated by quinine or atebrin, the more rapid the recovery and the less likelihood there is of relapse or development of pernicious symptoms.

In the endemic area of blackwater fever, and in persons who have left the area, large doses of quinine do sometimes undoubtedly determine an explosion of that dangerous disease, especially in cachectics.

Treatment of cerebral malaria.—In a cerebral attack ice-bags should be applied to the head at the same time as hot applications to the feet and legs ; the patient should be nursed in a semi-recumbent position ; artificial feeding may be necessary. No time should be lost in injecting quinine dihydrochloride intravenously, the average dose being 7–10 gr. dissolved in 10 c.c. of distilled water or normal saline. The injection should be performed slowly, at the rate of one minute per grain. Subsequent administration of 400 c.c. of reconstituted plasma or glucose saline by the continuous drip method, 40–60 drops per minute, helps to neutralize toxæmia. To bring the quinine solution into intimate contact with the parasites, adrenalin—10 minims of 1 in 1,000 solution—may be injected intramuscularly, or sometimes intravenously. If coma does not clear up, intravenous quinine must be continued in doses of 6 gr. 4–6 hourly, not exceeding a total of 30 gr. in 24 hours.

In coma or convulsions it must be remembered that œdema of the brain and increase of cerebro-spinal fluid ensue. Therefore, in comatose cases which do not clear up after intravenous injections of quinine, lumbar puncture and withdrawal of 20 c.c. or so of cerebro-spinal fluid may give relief. Rogan (1944) advised routine lumbar puncture in every case, if only to exclude cerebro-spinal meningitis ; but the two conditions may occur together. (Cordes performed puncture of the cisterna magna at the base of the brain, 50–60 c.c. of fluid being allowed to escape.) Increasing coma after intravenous quinine, especially if accompanied by signs of cerebral irritation, is due to multiple punctate subcortical hæmorrhages.

Thomas and Sydenstricker treated cerebral malaria by giving 2–4 litres of Ringer's solution subcutaneously during the first twenty-four hours to combat dehydration. Dextrose solution, 10 per cent., is given intravenously—500 c.c. every four to six hours. Quinine dihydrochloride, 0·5 grm., is added to the first dextrose injection and repeated every six hours until cerebral symptoms disappear.

Intravenous atebrin musonate in doses of 0·1 to 0·2 grm. is recommended by German authorities, but is not so instantaneous in action or so effective as quinine.

Treatment of hyperpyrexia.—Hyperpyrexia must be promptly met by prolonged immersion in the cold bath, rectal injections of iced water and ice-bags to the head. At the same time quinine must be injected intramuscularly, or intravenously. Prompt action in these cases is of the first importance, and may save life. If the temperature be kept down for three or four hours the quinine gets time to act on the parasites crowding the capillary vessels ; but if the temperature be allowed to mount and to remain high the patient is killed before the specific remedy has a chance. A cold bath, therefore, is absolutely necessary. In such circumstances, antipyrin and similar antipyretics are worse than useless. A good rule is to prepare to give the cold bath, or cold pack, if the axillary temperature reaches 106° F., and to remove the patient when the rectal temperature has fallen to 102° F.

Treatment of malaria-infected patients on return from the tropics.—If quinine or atebrin is being taken when the patient leaves the tropics for Europe, *their use, in the accustomed dose, should be systematically continued during the voyage and for a month or more after arrival.*

The importance of this practice cannot be too strongly stressed, especially when returning in the winter months. It has now become a routine—and it is a very wise one—to administer a prophylactic course of *atebrin* (mepacrine) for five to seven days to all those returning on board ship from West Africa and other endemic centres.

TREATMENT OF BLACKWATER FEVER

Patients who are suffering from or are threatened with hæmoglobinuria, who are in the *pre-blackwater state* (p. 77), or who have had this disease before should, on the slightest indication of fever, go to bed at once, keep the skin warm and scrupulously protected from draughts, and take plenty of warm fluid. If parasites are present in the blood, the patient should be treated with full doses of atebrin and an alkaline mixture ; if this drug is not available, small doses of quinine, commencing with 1 gr. twice daily, should be given, together with a moderate dose of calomel. Patients threatened with blackwater fever should not travel ; should it become imperative for any reason to move them, an injection of morphia should be given, or they may be kept under slight chloroform anæsthesia during the worst part of the journey. Burkitt in Kenya recommended intramuscular injection of sodium luminal, which kept patients quiet for two days. The principles of treatment should be based upon the appreciation of the underlying pathology of the condition, namely extensive hæmolysis, coupled with precipitation of insoluble acid hæmatin in the urinary tubules, plugging with cellular débris, and consequent damage and disorganization. Glucose, in large quantities by mouth and intravenously in 5 per cent. solution, is indicated, as it has been shown by Kubo and Kondo that it may prevent hæmolysis of red corpuscles by quinine.

As clinical evidence and certain experimental work indicate that suppression of urine is much less likely if the urine remains alkaline, massive doses of sodium citrate, either alone or with sodium bicarbonate, should be given until the urine is alkaline. It may be necessary to give as much as 1 drachm at four-hourly intervals. If the symptoms be more severe, intravenous injections of sodium bicarbonate, 150 gr. to 1 pint of distilled water, should be administered without delay (Hanschell). It is not advisable to inject more than one pint at a time, and it should be given slowly.[1]

If the urine still tends to be suppressed, *caffeine citrate*, 2 gr. twice in the twenty-four hours, should be given as a bland diuretic. In these circumstances hot fomentations should be applied to the loins, or cupping by Fenwick's glasses should be instituted, plenty of bland diluents administered, and an exclusive milk diet ordered until the albumin has disappeared from the urine. High rectal lavages with hot water have a marked diuretic effect, while Ross, in Southern Rhodesia, advocated lavage of the pelvis of the kidneys by ureteric catheters. After introduction of the catheters—a skilled manœuvre—a syringe containing 4 c.c. of warm sterile saline is attached and the fluid injected and again withdrawn about twelve times. In the mildest as well as the gravest cases, free and frequent administration of fluid is a most important measure, whether the patient is thirsty or not, and should be insisted on from the beginning of the attack. When, owing to persistent vomiting, fluid cannot be retained by the stomach, enemata of warm physiological *salt solution* (much less irritating to the bowel, and thus far more likely to be retained than plain water) should be administered repeatedly, 6–8 oz. every half-hour or hour, and in some instances Murphy's drip saline method *per rectum* is to be recommended. Turpentine stupes, mustard plasters and hot fomentations to the epigastrium are useful in controlling or ameliorating the vomiting; when severe, the time-honoured resort to sips of iced champagne is useful and agreeable. If insufficient fluid is being absorbed by the mouth, resort should be had to intrarectal or subcutaneous injection of normal saline by the continuous drip-method. The fluid is rapidly absorbed, and cannot fail to be useful in washing out infarcts which plug the renal tubules and bring about, or at all events contribute to, suppression of urine. In cases with convulsions or coma, injections of 5 per cent. *glucose solution* up to two or three pints are indicated. Marked restlessness may require minute doses of *morphia* ($\frac{1}{10}$ gr.); but the drug, of great use at times, must be employed with caution. For the very severe anæmia which results, intramuscular injections of liver extract, together with massive iron treatment by the mouth, are advocated.

---

[1] Maegraith and Havard (1944) claimed that intensive alkali treatment is dangerous, that it should be limited and that it should be controlled by estimation of the alkali reserve.

Blood transfusion has been successfully practised, and should be adopted in severe cases from the moment that hæmolysis commences. It has been shown abundantly that this is a natural procedure calculated to replace red blood-corpuscles which have been destroyed. Care must be exercised in grouping the blood, as the cells in these hæmolytic states are liable to auto-agglutination. Repeated transfusions can be employed, as much as 300–500 c.c. being given on each occasion. Wherever possible, drip transfusion methods should be used. There is no evidence to show that this arrests hæmolysis. With replacement of active functioning red blood-cells, urinary excretion is often rapidly re-established and the proportion of blood-urea falls to its normal level. In Southern Rhodesia, Blackie has stressed the great practical importance of this procedure. He considers it a life-saving measure and emphasizes that transfusions must be repeated until there is hæmatological evidence of active erythropoiesis.

It is advisable to give atebrin throughout the blackwater attack with the idea of preventing any possible relapse of malaria and to forestall any further hæmolysis. There may be, moreover, a superadded infection with *P. vivax*, *P. ovale* or *P. malariæ*, and cases are recorded in which one or other of those parasites have been demonstrated in the blood during convalescence. They should be regarded as concomitants, not as the exciting cause of blackwater. As the excretion of ascorbic acid is increased in subtertian malaria and in blackwater, this vitamin should be supplied in full doses, together with glucose, during the convalescent stages.

Nursing is most important in the management of blackwater fever. If the stomach will retain food, this should be given in a bland and fluid form, but there should be no attempt at forcible feeding, especially with rich and indigestible viands. One precaution against syncope must be sedulously enforced: the patient must not be allowed to sit up, much less to get out of bed, until food has been retained and assimilated, and the risk of sudden death has passed. The foot of the bed should be raised on blocks.

Usually a severe attack of blackwater fever extirpates the associated malaria infection; but this is not always so, and a relapse of fever with parasites in the blood is by no means uncommon. To guard against it, an after-course of atebrin treatment is always advisable.

If possible, the subject of blackwater fever should quit the endemic area, and never return to it or to any malarial locality; a severe attack, or a second attack, implying special susceptibility, should be regarded as a definite indication to leave the area.

PROPHYLAXIS OF MALARIA AND BLACKWATER FEVER

Anti-mosquito measures.—It is obviously impossible to wage war on all mosquitoes. Modern anti-malaria measures are based on the belief that it is more economic and effective to concentrate on the main malaria-carriers in each particular district—a procedure known as *species sanitation*. Some varieties enter dwellings and show preference for human blood and are said to be *anthropophilic*, but the majority are *zoophilic* and prefer to feed on domestic animals (*see* Appendix, p. 961).

The precipitin test is employed for the precise determination of the blood, human or mammalian, upon which captured anophelines have fed. The stomach blood is squeezed out on to filter paper, and rubbed well in. The paper should be divided into eight sectors, and blood drops disposed at the periphery. Such specimens can be stored for as long as 3–4 months in a dry place. Then sensitized sera, suitably diluted, are placed into tubes containing 3 c.c. of saline and the filter-papers containing the dried blood added. A positive reaction is shown by the development of an opalescent ring at the point of contact; it may appear at once or after incubating at 37° C. Tubes should be inspected at ten-minute intervals up to one hour. Control tests should be performed.

Other factors in planning antimalarial measures govern the principles. The distance between breeding places and dwellings is known as *distance of dispersal.* In the Oriental region a zone of half-a-mile radius free from breeding-places is found enough to protect a dwelling, but in the Ethiopian region this must be more extensive. Formerly it was thought that, generally speaking, about a thousand yards or one mile between a ship and a malarious shore would secure protection for the crew, but this does not always suffice, because Kligler has shown that, aided by prevailing winds, and especially during hibernation flights, the mosquitoes may travel five miles.

Killing off adult mosquitoes.—Light airy houses with plenty of ventilation, and with no dark corners, discourage the entry of mosquitoes; in the tropics most of the adult insects gain entrance during the night. Swatting the resting insects perched on roofs or walls of dwelling-rooms has been found very effective against *A. maculipennis* var. *atroparvus*, especially in Holland. Spraying the walls with an insecticide (Pyrethrum—Flit) once or twice a week has been found useful in India against *A. culicifacies*, especially during the autumn months and in cool weather. The "Freon bomb," a small round drum, containing pyrethrum concentrate dissolved in dichlorifluormethane, has been evolved by American Army hygienists. The substance is non-toxic and non-inflammable. On opening the nozzle the insecticide is blown out and forms a fine fog, or ærosol, which is projected 6–8 feet and kills all mosquitoes in 100,000 cubic feet. It is especially useful for ridding bedrooms and aircraft of mosquitoes. It is now apparent that D.D.T. is the most efficient insecticide.

Principles of species sanitation.—In this procedure measures are taken to prevent the breeding of dangerous species of *anopheles*; they must therefore be based upon an intimate study of the habits of each species. These measures may entail the drainage of swamps, if they can be incriminated, but they seldom can. In some cases it is more important to fill in holes and borrow-pits, to camber roads to prevent puddles, and to train the bends of streams or flush them periodically. Marshes, open to the sea, can be periodically flooded with salt water which kills off the larvæ.

In some species of the *Anopheles funestus* group, especially *A. minimus*, shading of streams prevents breeding but in this case the amount of overhead cover must be thick enough to prevent the growth of grass. To produce the right degree of shade, lantana (*L. aculeata*), basak (*Adhatoda vasica*), and duranta (*D. plumieri*) have been found suitable in northern districts of India, mugwort (*Artemisia vulgaris*) for tea, coffee, cardamom and rubber estates in the south.

To prevent mosquito breeding in *streams* and *waterways*, it is necessary to get as even and swift a flow as possible without eddies or backwaters. The stream should be canalized, that is to say, the sides should be sloped at an angle of 45 degrees. Embankments should be lined with large stones and the vegetation cleared from the edges. During the monsoon it is especially important to prevent the formation of pools after the subsidence of extra high flood. A stream thus treated is practically self-sterilizing, except with a species of anopheline such as *A. maculatus*, which is specially adapted for life in rocky streams. If necessary, canalization should be supplemented by oiling. Subsoil drainage can be employed in place of canalization and, indeed, forms an important feature of estate sanitation in Malaya. Flushing streams with automatic siphons is a modern method.

Seepage, or infiltration of water through bunds or dykes at the bottom of a hill foot, usually forms a fruitful breeding-ground for anophelines. *Running swamps* in the course of a stream in level country may form dangerous breeding-spots. They can be dealt with by oiling or Paris green. *Borrow-pits*, formed usually in the process of railway construction, may, when several years old, form suitable breeding-places. *Tanks*, in India and Ceylon, are seldom dangerous, but, if the margins are much overgrown with vegetation, certain anophelines may obtain a foothold.

Rice fields are dangerous when the water is kept in continuous motion through the fields; uncultivated plots in terraced fields that are allowed to become flooded are especially so. In Java the drying-off of the fields throughout a tract on one day each week has been made obligatory and is efficacious without apparently damaging the growth of the rice. To the inexperienced eye there might seem enormous potentialities for breeding anophelines in paddy fields, but the fields themselves are not always so much to blame as irrigation ditches.

Mangrove swamps, especially in the Andaman Islands and West Africa, are associated with virulent malaria due to the breeding of certain species of anophelines, especially *A. ludlowi* (*sundaicus*), and *A. gambiæ*, var. *melas*, in saline water. Sunlight also is necessary for the development of these larvæ. Thus, the dense virgin mangrove forest is healthy so long as it is daily traversed by tides; but when trees are cut down, or when bunds are constructed to interfere with tidal movements, and derelict pools are formed which are gradually diluted by rainfall to a suitable salinity, the breeding of anophelines takes place. Drainage is difficult at sea-level unless there is a big tidal range. In Malaya, owing to the sixteen-foot drop in the tides, it has become possible to install automatic sluice-gates to the bunds.

Smaller collections of water, if overlooked, may constitute a grave danger. A sagging gutter may hold enough water to support large numbers of larvæ; moreover, a good deal of atmospheric moisture is condensed upon the roofs of tropical bungalows so that the gutters are constantly being replenished even in the absence of rain. Holes in rotten trees may breed a limited number of anophelines; indeed one European species, *A. plumbeus*, breeds exclusively in this situation. In tropical Africa, *A. gambiæ*, the most active vector in the world, breeds in collections of water, small or large, of the greatest diversity. The most trivial road puddles, hoof marks or seepages may contain larvæ, as well as the larger collections. *Wells* are a certain source of trouble where they are built within native houses and where, in the absence of light, species of anophelines have adapted themselves. In Palestine and Macedonia they have been found to be the main breeding-place of *A. claviger*.*

Oil.—Oiling kills mosquito larvæ probably in several ways, but mainly by suffocation and its toxic action. The rapidity with which larvæ die depends upon the volatility and toxicity of the oil. Its spreading power can be improved by the addition of 1–2½ per cent. of castor or coco-nut oil. In Palestine Kligler found the most effective mixture to be 1 part of crude oil to 4 parts of kerosene, with the addition of 0·1–0·2 per cent. castor oil. *Anti-malarial oil* (A.M.M.) is a mixture containing diesel oil, solar oil and kerosene put up by the Asiatic Petroleum Co. Diesel oil is unrefined, and is added to give a lasting effect. *Malariol* is an approved mixture of petroleum with which a film is formed on the surface of the water. This is attained by allotting 2,750 sq. ft. to the gallon. By spraying the banks with this substance the grass may be destroyed, so that side pools and seepage are exposed. *Waste motor oil* has been used extensively in America. *Pesterine* is another mixture of oils, prepared by the Burmah Shell Oil Co. *Liquid paraffin* has been used by Swellengrebel and others in Holland. An almost colourless oil, it costs about £1 per cwt., and it is claimed that its effects are not vitiated by wind or rain, that it does not evaporate, is not toxic to fish, and that it does not prevent mosquitoes from ovi-positing.

Petrol, in the proportion of 24 oz. to every 80 sq. ft. of surface, is recommended for wells and tanks. It is claimed that larvæ are immediately destroyed and that the taste of petrol disappears in three hours.

---

* Formerly known as *A. bifurcatus*.

The following conditions are postulated for anti-larval oils as far as film stability is concerned :

(1) The main point should be quick penetration of the respiratory siphons of the larvæ—in not more than ten minutes.

(2) The oil should exert a direct toxic action on the larvæ and should change the flora of the streams.

The oil may be applied to the water in several ways. Spraying consists of forcing the oil under pressure through an atomizing nozzle from a special machine. Of the various patterns, the " Kent " sprayer best suits the capacities of the tropical labourer. Sprayers should be fitted with leather or flexible metal adjustments, as petroleum oil perishes rubber in a few days. For road-side ditches oil carts may be used, but for all purposes the knapsack sprayer is the most adaptable. The best oil for the purpose is a heavy oil which will issue from the sprayer as a fine cloud and spread uniformly over the water. Oil swabs, or cotton-wool steeped in oil and weighted down by a stone, when thrown into water are ideal for rock springs and running streams. Balls or " guddas " may be made of tow or sacking weighted with stones, and, after being soaked in heavy oil, are thrown into pools. The oil gradually oozes out and comes to the surface. A " gudda " is shaped like an ordinary pillow and is 28 in. long by 16 in. broad. It is made of sacking and will soak up about two gallons of oil and last about three months. In certain malarial districts in the United States oil-soaked sawdust has been found to give a more complete and permanent oiled surface, and this has the advantage of being easily transported. The oil gradually exudes and spreads as an even film over the surface of the water. In Panama drip cans and barrels are used from which the oil constantly drips from cork wicks or through holes from which nails project, but their value as an oiling agent is less than that of sprays. Oil must be applied at *seven-day intervals*.

Paris green is copper aceto-arsenite and, in the quantities used for anti-mosquito work, is harmless to other forms of life ; the particles are eaten by the anopheline larvæ and act as a direct poison ; culicine larvæ are not affected in the same manner as the surface-feeding anophelines ; fish are not killed. The powder should be intimately mixed with one hundred times its weight of finely-sifted dry road-dust, soapstone or powdered charcoal, and sown by hand, down wind, over the water at the rate of 170 grains of Paris green per ten square feet of water surface. The length of time the particles remain afloat depends upon the surface tension, and the more plentiful the vegetation the greater this is. In America (western Tennessee and northern Alabama), dusting machines have been invented for this purpose, and in large marshes the services of aeroplanes have been called on ; they fly at a speed of 60 miles an hour and at a height of 25–200 ft. One plane can cover 20 square miles a day with this substance, and an automatic distributing machine is now used. The water current effectually aids in spreading the dust in a canal up to 8 ft. deep. Paris green was the principal larvicide used in the great and successful campaign against *A. gambiæ* in Brazil.

Anopheles quadrimaculatus is the species most easily controlled by this method. The aeroplane designed for the purpose is a Stearman, model 4-D, open biplane with a 300 h.p. motor. The special equipment consists of a plywood hopper of 21 cubic feet capacity installed in front of the pilot's cockpit, so as to place the dust load as near the centre of gravity as possible. The cost of operating a dusting aeroplane works out at $40 per hour. Thirty-three acres per minute can be treated for $0.367 per acre, but perfect dusting weather conditions do not always occur. Aeroplane dusting for anopheles control on impounded waters is practical, effective and economic. In India, Brasier-Creagh advocated the D.H.83 Fox Moth as the most suitable machine, with structural modification, including a hopper and a Ventura tube. The pilot should wear a canvas suit and gas helmet. The cost works out at two to three shillings per acre.

Greenglide, a preparation made by Craven & Co., Evesham, has an advantage over crude Paris green in that it will float for weeks. Its composition is :

Arsenious oxide	55·37 per cent.
Copper oxide	31·12 ,,
Water-soluble arsenic	1·00 ,,

Copper sulphate is especially useful in tanks where water is stored for drinking purposes and where sheets of algæ are sheltering larvæ. Its action is not direct upon the larvæ themselves, but is one of starvation by killing off their food supply.

The prevention of mosquito breeding in uncovered and unscreened wells has peculiar difficulties. Oiling water with petroleum is apt to mar its taste. Williamson has recommended the liberation of gases and vapours. Paraformal (3 oz. per square yard) vaporized at the bottom of a three-foot shaft will kill anopheline larvæ in half an hour. Sulphur dioxide acts by acidifying the water. When using gases, wells should be closed, and for this purpose a portable parachute to be lowered into them has been devised.

Larvivorous fish of some suitable local or well-known foreign species can be introduced. A favourite is the " millions " (" Millions-fish " ; *Lebistes reticulatus* of the Indies), or " top minnow," *Gambusia*, which is a surface feeder, capable of withstanding heat and cold, and also viviparous and cannibalistic. In pools, weeds must be cut away to give the fish access to the larvæ. This method is efficacious in temple wells and pools in Bombay against *A. stephensi*, and in the Adriatic Islands against *A. maculipennis*.

Mosquito-netting.—Mosquito-netting should contain 25 to 26 holes to the square inch (Fig. 11). The best is known as " bobbin " netting, woven of 30's cotton (by which is meant that 1 lb. of the thread will reach 30 times round a circumference of 840 yards). The square inch of the trade does not correspond to that of the mathematician ; it means that the count is made along two lines of holes which fall within the opening of one inch square. Therefore, there are some 150 holes to the square inch (Fig. 12).

The main points in efficiency are that the holes should not be too large ; that the net should not be so narrow as to permit knees and elbows to be bitten through the netting, and that the sides should be deep enough to be tucked in securely. When two single beds are used occupants can be protected efficiently as follows :—The beds are placed close together and the intervening space covered with a single sheet, placed immediately over the mattress and beneath

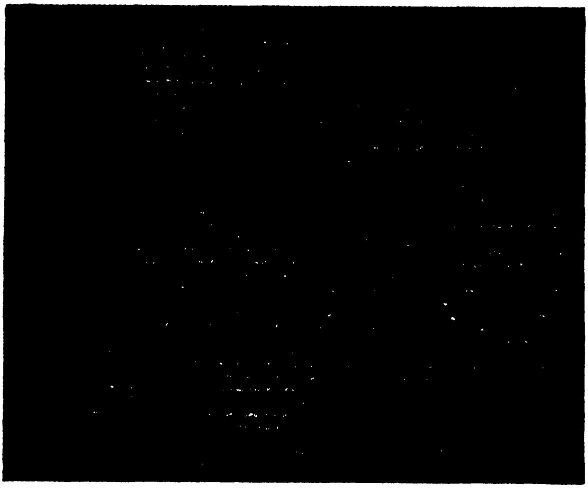


Fig. 11.—Mosquito-netting, 25/26 holes to the sq. inch.
(*MacArthur, Jl. R.A.M.C.*)

the other two sheets. The net itself should be suspended from the framework, or attached by tapes to rings hung on three wires and stretched across the room. When a mosquito is found inside the net it can be destroyed with ease by passing a lighted candle downwards about three inches from the insect when it will *fly back* into the flame. If the edges of the net are not tucked in, they must be so weighted that they touch the floor, so that the insects cannot crawl underneath.

During the daytime the net should be rolled up so that it contains no mosquitoes when set up for the night. Light attracts mosquitoes ; for this reason blinds should be drawn down before turning on the light.

Mosquito boots of soft leather or canvas—or Wellington boots—protect the ankles and legs in the evening ; for ladies, a pillow-case drawn up over the legs and feet is a useful precaution. *Anti-mosquito veils and gloves* (*or gauntlets with sleeves*) are used to protect soldiers and others on night duty.

Mosquito repellents.—*Fumigation.* Chinks in doors and windows should be closed ; one window only should be left uncovered, and a white sheet should be placed on the floor in front of it. The mosquitoes, being stupified by fumigation, will fall on the sheet and then can easily be seen, swept up and burned. For this purpose various substances have been recommended, of which pyrethrum powder is probably the most effective. Pyrethrum powder (*Pyrethri flores*) is made from the dried flowerheads of the pyrethrum. It forms the chief

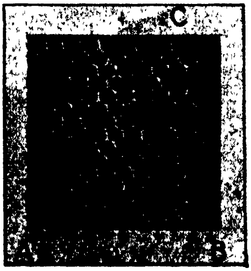


Fig. 12.—The correct method of counting the mesh of cotton netting. The mesh of this net is the sum of the counts made along the lines A B and [illegible] counted twice. (*Jl. R.A.M.C.*)

ingredient of many insect powders and sprays (*e.g.* Flit). The powder may be used dry and puffed into the air of the room.[1] For domestic use a handspray is necessary, but in dormitories and barracks a proper nebulizer is advisable.

Many proprietary sprays are on the market, most of them having a basis of kerosene oil and pyrethrum. The following may be mentioned : Phantomyst, Flytox, Shell-tox, Desquito, Whiz, Flyosan, Fly-ded, Necrosene, Rids.

The cost of these preparations is so high that most sanitarians use a locally-prepared mixture, such as that of Brug and Van Slooten (a mixture of kerosene with 2 per cent. of *carbon tetrachloride*) known as " rids." Sprays of this nature must not be used in the vicinity of naked lights. There is usually a very considerable movement of anopheles in and out of buildings, so that spraying must be repeated at frequent intervals (3–4 days). The formula of several sprays is as follows :

(1)	Army Fly Spray :	
	Ext. of pyrethrum	1 part
	Kerosene	64 parts
(2)	For aircraft :	
	Army Fly Spray	40 parts
	Lethane 384 special	3 „
	Kerosene	97 „
(3)	Oil of wintergreen	1 part
	Kerosene	99 parts
(4)	Carbon tetrachloride	2 parts
	Kerosene	98 „

Recent experience suggests that spraying clothing and mosquito nets with *dimethyl phthalate* is likely to prove most efficient.

For personal use many oils and ointments have been advocated ; they are smeared on the hands and face. The proprietary preparation known as Sketofax is recommended by many. Bamber oil has a big reputation ; this consists of oil of citronella 1¼ parts, kerosene 1 part, coco-nut oil 2 parts, made up with 1 per cent. carbolic acid as a preservative.

As oil of citronella, used as a mosquito-repellent, often irritates the skin, the following formula (Army official anti-mosquito cream) has been found to be effective, it acts as repellent for 1½ to 2 hours, but is greasy and dirty ; it rubs off quickly.

Oil of citronella	20 per cent.
Paraffinum molle	53·25 „ „
Paraffinum durum	26·75 „ „

The paraffin should be melted and other constituents then added. The mixture being well stirred, it should be bottled and cooled rapidly, preferably by placing the bottle in a basin of cold water. It is also useful for sandflies.

Stearin cream gives 97 per cent. protection for eight hours. It is not greasy but is unstable.

Stearin	16 per cent.
Water	69 „ „
Glycerin	4 „ „
33 per cent. ammonia in water	0·9 „ „
Pryethrum extract 2% total pyrethrins	10 „ „

---

[1] For further details the reader is referred to " Malaria Control by Anti-mosquito Measures," by Gordon Covell. Thacker, Spink & Co.

New American preparations:

(a) Indalone 25 per cent. in arachis oil, applied with sprinkler container.

(b) Dimethyl phthalate: liquid oil used neat as vanishing cream; protects 1–2 hours: considered a most excellent repellent.

(c) Rutgers 612; popular in America.

(d) D.D.T. (dichlordiphenyl trichlorethane: this can be used as a larvicide and as a spray against adult mosquitoes. It is made by heating together chlorbenzene, chloral and sulphuric acid, and seems very effective. For further information *see* p. 233. For killing adult mosquitoes the spray may be mixed with pyrethrum. A solution may be applied to interior walls or incorporated with paint. For larvæ, 5 per cent. solution is active—2 quarts per acre for local spray and ½ lb. per acre for spreading by aircraft. The chief advantage lies in its residual action. Much more work on dosage is necessary. Its action appears to vary with species, subspecies and conditions, so that each district requires separate consideration.

These all act as repellents against other insects, including *Trombicula.*

Burning incense sticks, such as Katol, tends to keep mosquitoes away. They are especially useful under tables where mosquitoes congregate.

The irritation of a bite may be allayed by rubbing the puncture with a moist cake of soap, or by applying 1 per cent. alcoholic solution of menthol, or a 1 : 20 carbolic solution. Hydrogen peroxide or weak ammonia solution is also useful.

A dilute solution of magnesium sulphate, 1 ounce to 10 ounces of water, applied to the skin is said to act as a preventative against mosquito-bites; it has the advantage of being cheap and not irritating. The juice of a fresh-cut lime fruit rubbed well into the skin and allowed to dry is an excellent preventative.

These measures are undoubtedly of some value, but they are tedious and sometimes disagreeable to apply, and must only be looked upon as adjuvants to other measures to protect from mosquito-bites.

CHEMOPROPHYLAXIS OF MALARIA

Quinine is regularly taken in most tropical countries as a prophylactic or suppressive of malaria, and, though it has considerable value, the protection afforded cannot be considered absolute. Celli's figures for the relative value of prophylactic measures are as follows:

Mosquito protection plus quinine prophylaxis	1·76	per cent.	infected
Mosquito protection alone	2·5	,,	,,
Quinine prophylaxis alone	20	,,	,,
No protection at all	33	,,	,,

Under war conditions quinine prophylaxis has not proved satisfactory, so that with troops in open warfare it should not be solely relied upon, but it may be the only protection possible.

Five grains of quinine hydrochloride, preferably in liquid form, should be taken at sundown, some two hours before retiring, during the malaria season, or, according to Koch's system, 15 gr. twice weekly, or on two consecutive days over the week-end. In regular quinine-takers the clinical phenomena of subtertian malaria are mitigated and the chances of developing blackwater fever thereby reduced. In the present war the dosage recommended above is considered insufficient; 10 gr. daily is now advised, to be commenced on entering the hyperendemic area and continued one month after leaving.

Experimental scientific evidence of quinine prophylaxis is not so satisfactory. Thus, Yorke and Macfie showed that sporozoites injected by an infected mosquito are not harmed, even when the patients are taking 30 gr. of quinine daily. Neither does quinine appear to have any direct action upon plasmodia in the trophozoite stage. Mühlens and Kirschbaum mixed malaria blood with a solution of quinine, 1 in 10,000 (left in contact for twelve hours), and were still able to infect a volunteer by direct inoculation. *Anopheles maculipennis* developed malarial oöcysts after feeding on a malaria subject who was on full doses of quinine.

Plasmoquine.—The fact that plasmoquine attacks the gametocyte stages of plasmodia raised hopes that it would prove the ideal prophylactic. Under experimental conditions James has shown that the incubation period of benign tertian malaria can be postponed by this method from three to six months. The amount of this drug necessary to prevent infection ranges from 0·06–0·08 grm. daily, and this must be given at least three days before and five days after the infecting bite; these doses are near the toxic limit and cannot be well tolerated in tropical countries.

Quinoplasmine, 0·02 grm., twice weekly to adults and proportionately less to children, was claimed by Mosna to reduce the general morbidity and incidence, especially amongst small children.

Atebrin (mepacrine hydrochloride, quinacrine), in doses of 0·3 grm. daily, taken over a period of 5–7 days before being bitten by infective mosquitoes, appears to exert an influence on the sporozoites, and the incubation period of a malarial attack may be considerably prolonged (to thirty-seven weeks, James and Shute), though in larger doses Shute has now shown that it either prevents penetration of sporozoites or destroys them when they have once entered the skin. This method is now known as *causal prophylaxis*. To be completely effective the doses are considerable, and range, in the experiments so far recorded, from a total of 6–8 grm. over a period of 22 days before, and 30–60 days after exposure to infection.

Clinical or suppressive chemoprophylaxis.—Under field conditions weekly doses of 0·4–0·6 grm. of atebrin are considered sufficient and do not interfere with the general health. Some prefer to take it in one dose of 0·2 grm. on Wednesday and a similar dose on Sunday.

Children may be given weekly:

Up to 2 years . .	0·05 grm.	(half a tablet)
2–4 years . . .	0·075 ,,	(three-quarters of a tablet).
5–8 years . . .	0·1 ,,	(one tablet)
Over 8 years . .	0·2 ,,	(two tablets)

The reports on this method of suppressing clinical malaria in Malaya have been encouraging (Hoops). In West Africa Hill advocated daily doses of 0·1 grm., with the exception of Sundays, taken prophylactically as a protection for British troops; ill effects were not noted and the protection was good. It should be commenced at least one week before entering the endemic area and continued for one month after leaving, and this course is now recommended as superior to quinine.

That atebrin acts as a causal prophylactic in malaria can be judged by:

(*a*) the continued absence of clinical symptoms of malaria.

(*b*) the continued absence of malaria parasites in the peripheral blood.

(*c*) the stability of the hæmoglobin index, in spite of exposure to malarial infection.

Much recent information on atebrin prophylaxis cannot yet be published. The important factor is the atebrin level of the blood ; to be effective, this should be between 25 and 30 microgrammes (γ) per litre of plasma[1] ; or 2·5–3γ per 100 c.c. ; 25 c.c. of blood are required for the test. Under active service conditions in troops, this level is much influenced by sweating, or by too rapid elimination in the urine. It seems that, when once the level has been lowered, malarial infection can break through, and parasites appear in the peripheral blood in large numbers, but if atebrin is then given in therapeutic doses (0·6 grm. initial dose, followed by 0·3 grm. daily), the trophozoites once more disappear. But it has still to be settled whether in suppressive doses atebrin is invariably harmless under conditions of active service. Some military authorities have asserted that it may give rise to debilitating diarrhœa or abdominal pain, which it does not do under more sedentary conditions. There is no evidence that the administration of atebrin in suppressive doses (0·6 grm. weekly) for a period up to one year causes liver or renal damage.

General considerations.—Clark and his colleagues, as the result of ten years' experience in drug prophylaxis in Panama, considered that even when atebrin, quinine or plasmoquine are given to all persons found infected at monthly surveys, it is impossible to eradicate malaria parasites entirely, or even reduce them to a point at which transmission is greatly lessened. Drug prophylaxis, conducted in this manner, is powerless to prevent epidemics if unusually large numbers of anophelines are present, but *severe* clinical malaria can be almost eliminated. Field and Niven remarked upon the rapid reappearance of clinical malaria after suspension of prophylactic drugs, especially in Indian labourers, and they concluded that effective drug prophylaxis is not consistent with the acquisition of effective immunity.

---

[1] γ = 0·0001 grm.

CHAPTER IV

HUMAN TRYPANOSOMIASIS

Definition.—Diseases produced by parasites of the genus *Trypanosoma*, characterized by irregular and chronic fever, skin eruptions, local œdema, adenitis, physical and mental lethargy, and sometimes death. The trypanosome is spread by the tsetse flies (*Glossina*) in Africa, and by winged bugs (*Reduviidæ*) in Central America.

The trypanosomes are blood parasites which are widely distributed in animals, especially in big game, in the countries in which these diseases occur. These animal hosts act as reservoirs of the trypanosomes which cause disease in man. The geographical distribution of human trypanosomiasis is shown in Map I; that of the African forms in Map II.

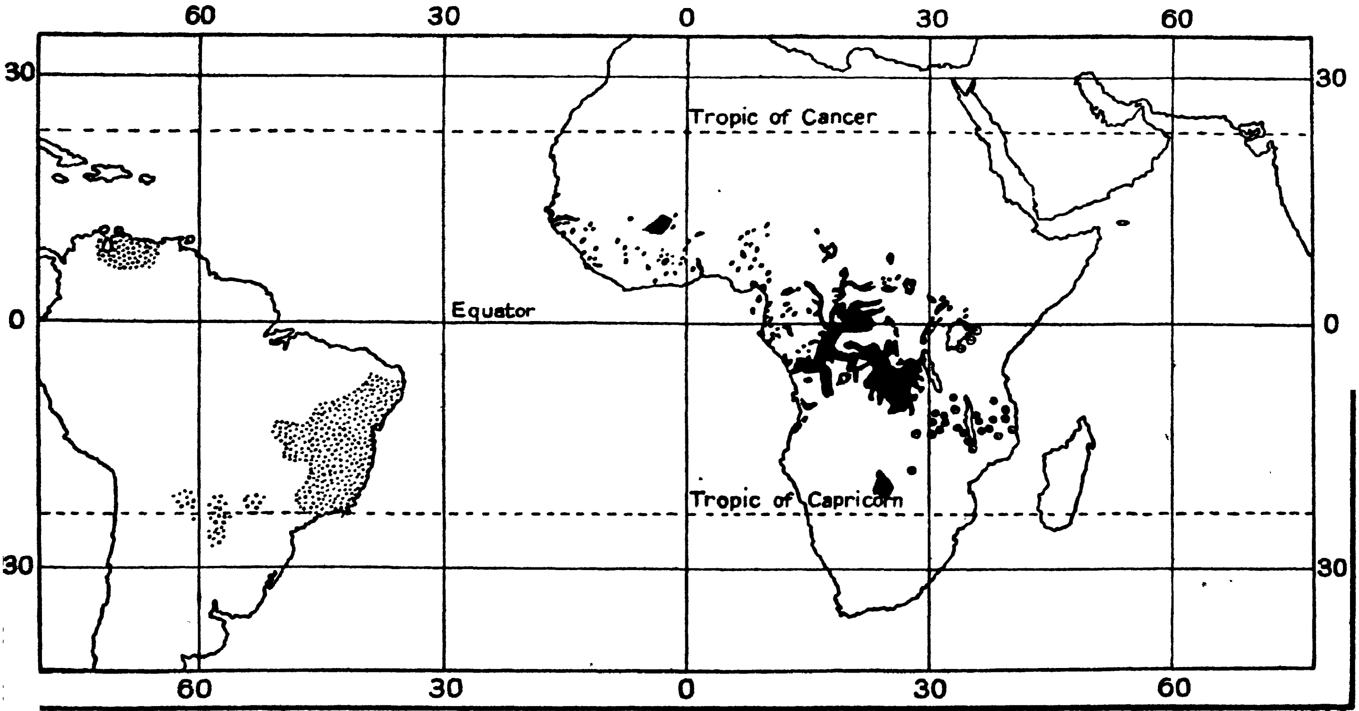
I. AFRICAN HUMAN TRYPANOSOMIASIS

History.—Human trypanosomiasis, or sleeping-sickness, has been known for well over a century, but it was not until some forty-two years ago that the pathogenic cause was definitely recognized. In 1901 Forde encountered a trypanosome in the blood of a European suffering from fever in Gambia. In 1902 Dutton found a similar organism in the blood of a native of that colony, and suggested the name *Trypanosoma gambiense* for the parasite. In 1903, C. J. Baker recorded the presence of trypanosomes in the peripheral blood of natives of Uganda and associated their presence with that of the tsetse fly. Later in the same year trypanosomes were found in the cerebro-spinal fluid as well as in the blood of sleeping-sickness cases in Uganda, and were proved to be the cause of all the manifestations of this disease by Bruce, Nabarro and others (Fig. 14.) What is believed to constitute a separate species, *T. rhodesiense*, was recognized by Stephens and Fantham (1910), and this form has a distinct geographical distribution.

GAMBIENSE SLEEPING-SICKNESS

Geographical distribution (Map II).—The distribution of this disease corresponds roughly with that of the tsetse flies, *Glossina palpalis* and *G. tachinoides*. It is found in scattered areas on the Gambia, in Sierra Leone, the Gold Coast, Nigeria, Cameroons, the Southern Sudan, and Uganda; but its main stronghold is along the waters of the Congo and its branches. In the Sudan an endemic focus existed in the Bahr-el-Ghazal Province, but has greatly diminished in extent, though *Glossina palpalis* is found in a belt, 1,000 miles long, ranging towards Darfur. The most southerly focus in Africa has been found in the Okavango and Chobe swamps in Ngamiland, on the borders of the South African Union. The League of Nations stated that over a million cases of sleeping-sickness are treated every year.

Ætiology.—Neither age, sex, occupation, nor race *per se* has any influence on the susceptibility to trypanosome infection, except in so far as those factors conduce to opportunity. Thus, Schwetz found a baby of twenty days old infected in the Belgian Congo. Occupation (boatmen, fishermen, water-carriers) conduces to infection, if it entails frequenting the waterside haunts of the glossina. In common with other trypanosomes,



Geographical Distribution of Trypanosomiasis

■ = *T. gambiense* ● = *T. rhodesiense* ⁘ = *T. cruzi in man*

MAP I

T. gambiense (Fig. 13), as seen in fresh blood, is an active, wriggling organism, having a spindle-shaped body which is slightly compressed laterally and spirally twisted. Dividing forms are sometimes met.

There is no uniformity in the number of parasites in the blood: sometimes they are fairly abundant, one or two in each field of the microscope; at other times, and in the same patient, it may be difficult or impossible, even after prolonged search, to find a single specimen; in some instances they tend to recur cyclically at intervals of a week or more. On the whole, although with exceptions, the parasites are most abundant in the blood during the febrile attacks. Apparently the blood is not their only or their principal habitat. They are usually found easily in enlarged lymphatic glands, and have been seen also in the cerebro-spinal fluid, serous cavities, and in the substance of the solid organs, including the brain, where they are distributed throughout the tissues outside the blood-vessels.

The parasite may be cultured on N.N.N., or better still the Razgha-Reichenow medium (*see* p. 1017). It can usually be inoculated into most mammals, including all the ordinary domestic and laboratory animals, and is especially pathogenic for the rat, but shows considerable variations in virulence. Monkeys, especially *Erythrocebus patas*, and dogs are susceptible, while amphibia and reptiles are immune. Inoculation of susceptible animals may be used to demonstrate the parasites when they occur in very scanty numbers in the peripheral blood, and is sometimes successful in those rare cases where they cannot be found after careful microscopical examination.

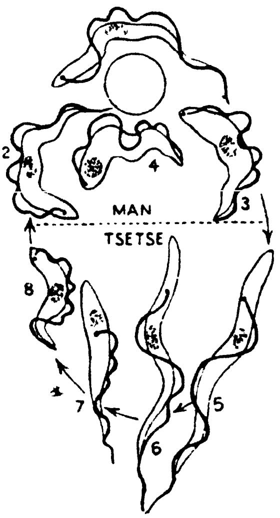


Fig. 13.—Life cycle of ***Trypanosoma gambiense*** **and** ***T. rhodesiense.*** ***(After C. A. Hoare.)***

1—4. Trypanosomes in human blood (1, Long, slender form; 2. Intermediate form; 3. Short, stumpy form; 4. Stumpy form with posterior nucleus).

5—8. Stages in the tsetse fly (trypanosome forms 5, in stomach, and 6, in proventriculus; 7, Crithidia, and 8, Metacyclic trypanosomes in salivary glands).

Red blood-corpuscle drawn to scale.

As shown by Laveran and others, these trypanosomes undergo agglomeration, both in blood and in artificial cultures, when exposed to unfavourable biological conditions.

How long a trypanosome infection may persist in the human body has not been definitely determined, but there is direct evidence that it may continue for many years. From what we know of the incubation period of sleeping-sickness, it is not improbable that this period may extend to seven years or longer.

Transmission.—*T. Gambiense* is not usually transmitted hereditarily in human beings, although the organisms have been found in the placental blood of infected rats, as well as in the livers of their embryos, but as in malaria and kala-azar, intra-uterine congenital transmission has occasionally been noted, and in Germany there is a record of one case in a European child born in Hamburg (Mühlens).

In the French Congo, Darré and his colleagues recognized hereditary trypanosomiasis and demonstrated trypanosomes in the cerebro-spinal fluid of a child born of an infected mother. David and Pape (1942) described two cases in the French Cameroons where transplacental transmission was established, trypanosomes being found in the blood of the infants as well as in that from the umbilical cord.

Rôle of the tsetse fly as transmitting agent.—There is no evidence that biting flies other than the tsetse are concerned in the spread of human trypanosomiasis, but there are apparently two methods by which this fly is able to transmit trypanosomes : (1) cyclical, and (2) mechanical.

(1) *Cyclical transmission.*—As originally demonstrated by F. K. Kleine in 1909, *T. gambiense* undergoes an endogenous cycle of development in the circulating blood of the vertebrate. Certain short forms are regarded as the adult or metacyclic type, and they alone are responsible for carrying on the exogenous cycle. When ingested by the fly trypanosomes first multiply in the mid-gut ; if the contents of the intestine at this stage are injected into the susceptible animal, they do not convey infection. After a cycle of development, lasting 12–20 days, the infective forms of trypanosomes congregate in the salivary glands. An important part is played by the peritrophic membrane lining the gut of the fly. (For further details, *see* p. 855.)

There is no doubt now that transmission ordinarily occurs through the bite of infected flies, trypanosomes passing through the salivary duct as do the sporozoites of the malaria parasite. The adaptation of *T. gambiense* to *G. palpalis* is remarkably specific. In Western Nigeria and in certain districts of the Gold Coast, however, *Glossina tachinoides* is naturally infected and is mainly responsible for epidemics of sleeping-sickness in those countries. There is no evidence that the tsetse can transmit the trypanosome to its offspring.

Van Hoof, Henrard and Peel found that the index of cyclical transmissibility of trypanosomiasis on the Congo can be calculated by the formula :

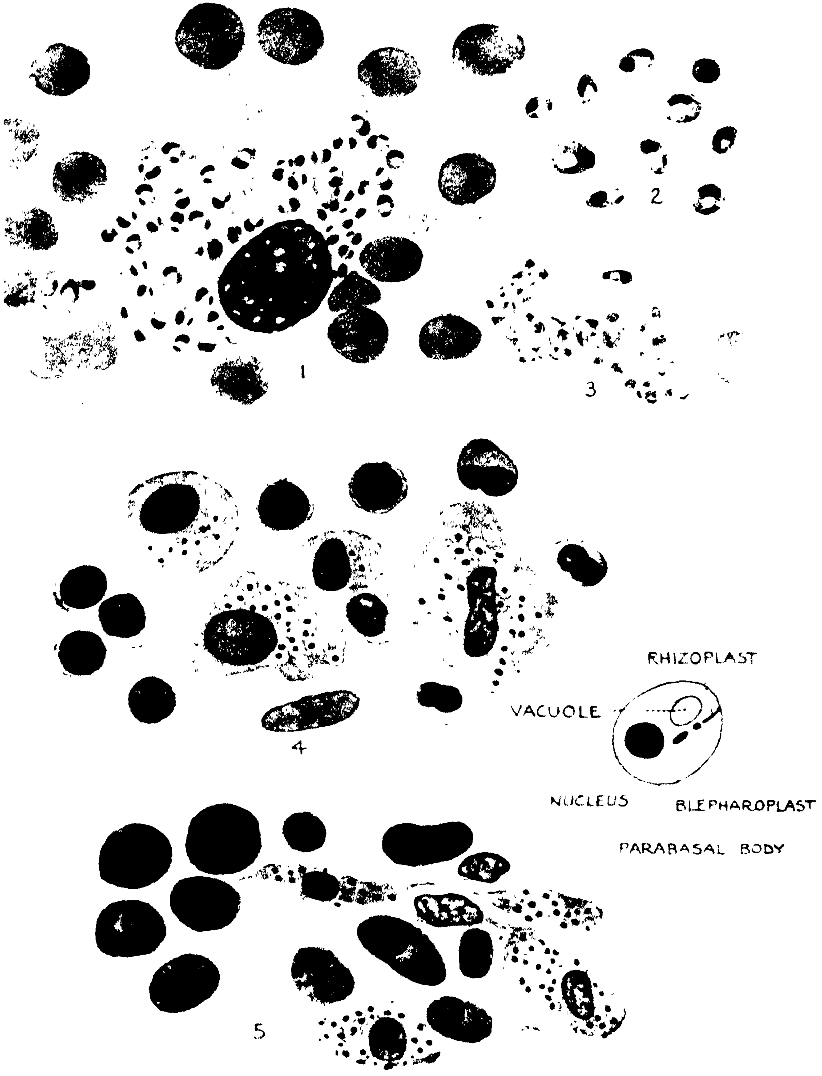
$$I = \frac{g}{i} \times \frac{n \times 100}{N} \text{ where—}$$

I = index of cyclical transmissibility.
g = number of glossina with trypanosomes in salivary glands.
i = number of glossina which after the fifteenth day of the experiment were found to harbour trypanosomes.
n = the total number of glossina found during the whole experiment.
N = number of glossina dissected during the experiment.

The mean index of transmissibility for the Congo is 3·68 ; the index of infectivity is 6·17, and the metacyclic index is 0·61 per cent.

(2) *Mechanical transmission.*—Duke, in Uganda, suggested on epidemiological grounds that mechanical transmission by the glossina of a virulent strain of *T. gambiense* from man to man might be responsible for some epidemics.

Reservoir-hosts.—In the plateau province, Northern Nigeria, Taylor found that, in the absence of game and suitable aquatic reptiles, which

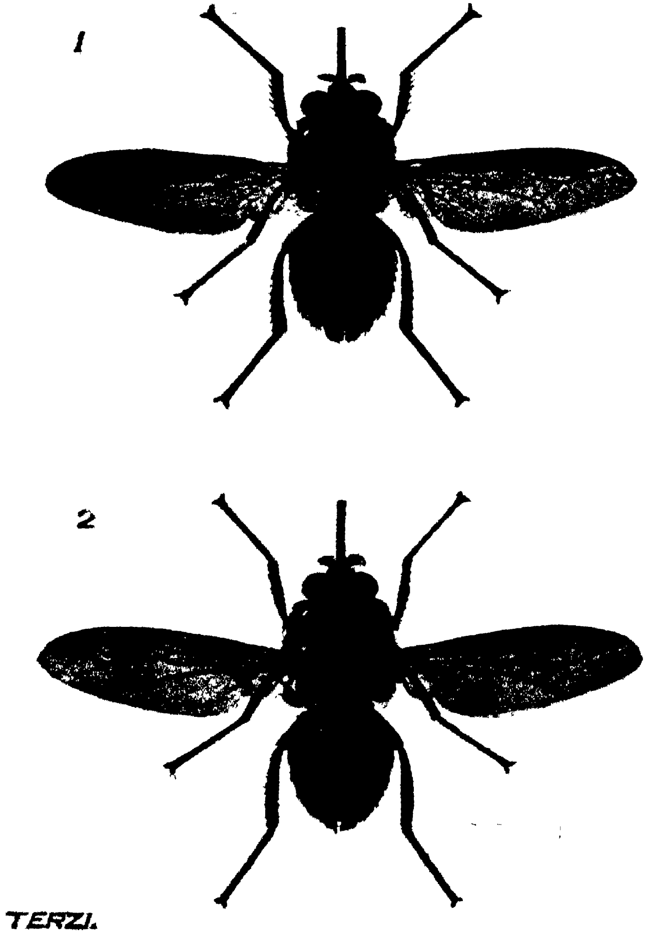


1, Parasites enclosed in endothelial cells in film from spleen puncture, stained with Leishman. 2, Free forms from spleen. 3, Blood-platelets in same film for comparison. 4, Parasites enclosed within splenic pulp cells, as seen in section, stained with hæmatoxylin. 5, Parasites in histiocytes and endothelial cells in intestinal mucosa. 6, Diagram of Leishman-Donovan body, highly magnified.

LEISHMAN-DONOVAN BODIES IN KALA-AZAR.

× 1,000

PLATE IV



1, *Glossina palpalis.* 2, *G. morsitans.*

TSETSE-FLIES.

PLATE V

form normal buffers, the fly feeds for the most part on man. Shade, which is only found near villages, is also important. These two factors combine to bring man and fly into close contact, and the rate of trypanosome infection of the fly is correspondingly high. In Uganda the same conditions obtain. Wild game may sometimes act as reservoirs. It has been proved that eleven common species of antelope (bushbuck, reedbuck, and waterbuck) can be inoculated with *T. gambiense* by subjecting them to the bites of experimentally-infected tsetse flies; furthermore, it has been established that certain marsh-haunting antelopes, especially the situtunga—Speke's antelope (*Limnotragus spekei*)—are commonly infected under natural conditions with *T. gambiense*. Thus, Duke found that they remained infected in the islands of Victoria Nyanza four and a half years after the evacuation of the human population.

Domestic stock must be now considered as a reservoir of infection for man, since *T. gambiense* has been found by various observers in oxen, goats and sheep. Van Hoof stated that in the Belgian Congo domestic pigs form ideal reservoir hosts, but show no obvious ill effects themselves.

Pathology.—The chief lesions are in the lymphatic glands of the neck, submaxillary region and mesentery and in the central nervous system.

Central nervous system.—Typical pathological lesions are seen only when pathogenic trypanosomes have invaded the central nervous system. No gross lesions of the nerve centres are present, but there is progressive

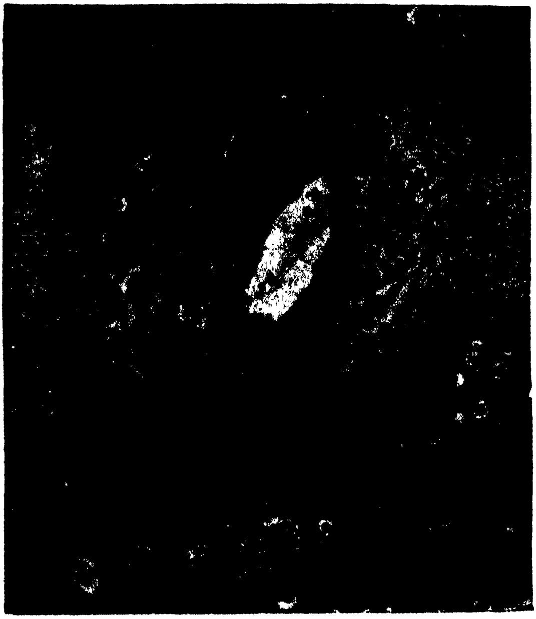


Fig. 14.—Section of brain in sleeping-sickness, showing round-cell infiltration filling perivascular space. (*Dr. A. C. Stevenson, " Trans. Roy. Soc. Trop. Med. and*

chronic leptomeningitis, especially in the Virchow-Robin space (where the pia runs alongside the blood-vessels and the fluid acts as lymph), and also on the vertex (Dürck's nodes).

The dura may be adherent to the skull and to the arachnoid. The brain itself is congested and œdematous, the surface smooth, with convolutions flattened by increased pressure. The consistency of the brain tissue is unaltered, except for softening around any hæmorrhages that may occur. The ventricles are distended with fluid. In all cases there is perivascular lymphatic tissue (perivascular cuff) throughout the brain tissue and meninges, varying in amount and in different anatomical regions (Fig. 14). The invading cells are glia cells, lymphocytes, the morula (Mott) and Marshalko cells. The two latter types are degenerative plasmocytes. Morula cells stain deeply, with unilateral oval nucleus and vacuolated protoplasm; Marshalko cells are large plasma cells with a blue polar zone round the nucleus, with surrounding halo and acidophilic protoplasm.

As originally demonstrated by Wolbach in experimental animals and by Stevenson in man, in advanced cases lesions in lymphatic glands and in brain are caused by invasion of the solid tissues by trypanosomes which have migrated from the bloodstream. In the brain they have been found mainly in the frontal lobe, pons and medulla, aggregated together in masses or nests without definite relation to blood-vessels. (Fig. 15.) The organisms also invade the cerebro-spinal fluid; they enter the canal from the choroidal plexus where they congregate, as Peruzzi has shown, in active stages of division. Optic atrophy due to trypanosomiasis has been recorded.

The essential pathological features of cerebral trypanosomiasis recall a somewhat similar condition in general paralysis of the insane and disseminated sclerosis. Thus, the lumen of the vessels is contracted and the walls thickened. The cells of the spinal cord usually show fewer changes than those of the medulla or cortex. The endothelium of the capsules of the spinal ganglia is proliferated and there is infiltration of the trabeculæ with lymphocytes and plasma cells. The spinal canal may be blocked by cell proliferation. The cerebro-spinal fluid in early cases is under increased pressure (30–100 cm. of water); the total proteins being very much increased, to 1 grm. per litre (normal 0·2 grm.).

The cells are increased to 15 to 500 or more per c.mm. (normal 2–3) and comprise lymphocytes, mononuclears, morula cells, eosinophils and trypanosomes.

Kidneys.—There is glomerular nephritis, leading to fibrosis, also a generalized proliferation of the reticulo-endothelium in the capillaries.

Heart.—Ecchymoses and even large hæmorrhages in the epi- and endocardium have been observed. Peruzzi has shown (in the pathology of experimental trypanosomiasis in monkeys) that severe myocarditis is frequently present and is due to masses of trypanosomes within the muscle cells.

Liver.—There is spoiling of parenchyma cells, probably from toxic absorption, associated with depletion of the blood sugar.

s.—These are characterized by intravascular proliferation of the reticulo-endothelium, which may block the capillaries with fibrosis, and collapse of the alveoli.

Bone marrow.—The fat is reduced and the whole tissue may be gelatinous and homogeneous.

Skin.—Localized œdema, due to collections of lymphocytes, is observed in the eyelids, perineum and skin of the back.

The *spleen* is slightly enlarged. The Malpighian bodies are few and inconspicuous. There is a general proliferation of the reticulo-endothelium, congestion at the periphery of the splenic sinuses, often focal necrosis with endothelial macrophages and ingested red blood corpuscles. Giant cells have been observed.

Lymphatic tissue shows general hyperplasia. The glands are enlarged, soft and fusiform, with great proliferation of the lymphocytes. At first there is increase of large mononuclear cells, lymphocytes and later fibroblasts. They are very vascular, with small hæmorrhages containing trypanosomes (which can therefore be easily demonstrated by gland puncture).

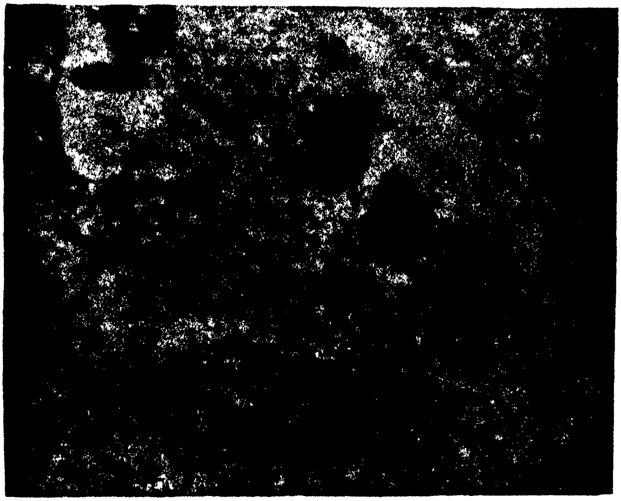


Fig. 15.—Photomicrograph of frontal lobe of brain in sleeping-sickness, showing trypanosomes in grey matter. (*Dr. A. C. Stevenson, "Trans. Roy. Soc. Trop. Med. and Hyg."*)

The *blood* shows definite anæmia due to toxæmia and erythophagocytosis. The hæmoglobin is reduced and colour index below normal. There is usually auto-agglutination of red cells with rouleaux formation. The alkali reserve is diminished and blood sugar low.

Symptoms.—The *incubation period* of the glossina-conveyed disease and that resulting from direct artificial inoculation seem to be about the same, from two to three weeks in dogs, horses and monkeys. From experience of infected Europeans, in whom the dates can be controlled, it appears to be about fourteen days. The bite of an infected glossina is followed, in a proportion of cases, by local irritation of greater or lesser severity. This has been called the "trypanosome chancre" and is described as a red nodule surrounded by a white waxen zone. It subsides in a few days, to be followed, sooner or later, by fever, which may last a week or longer, and may be accompanied, in Europeans at all events, by a peculiar type of erythema and a certain amount of serous connective tissue infiltration (Plate VII, Fig. 1). The trypanosomes appear in the peripheral blood about twenty-one days after the infecting bite. A form of hyperæthesia, known as "Kerandel's sign," is usual, though not invariable; when the patient strikes any hard object he suffers discomfort amounting to actual pain after a slight delay. In time the fever subsides more or less completely, to recur at irregular intervals of days or weeks. It is sometimes mild, sometimes severe, and occasionally hyperpyrexial (106·6° F.), the evening temperature being always the highest. It may last for weeks and the apyretic period may be equally prolonged, or it may be continuous. The fever and all other clinical manifestations of trypanosomiasis are irregular in intensity and duration. In time the

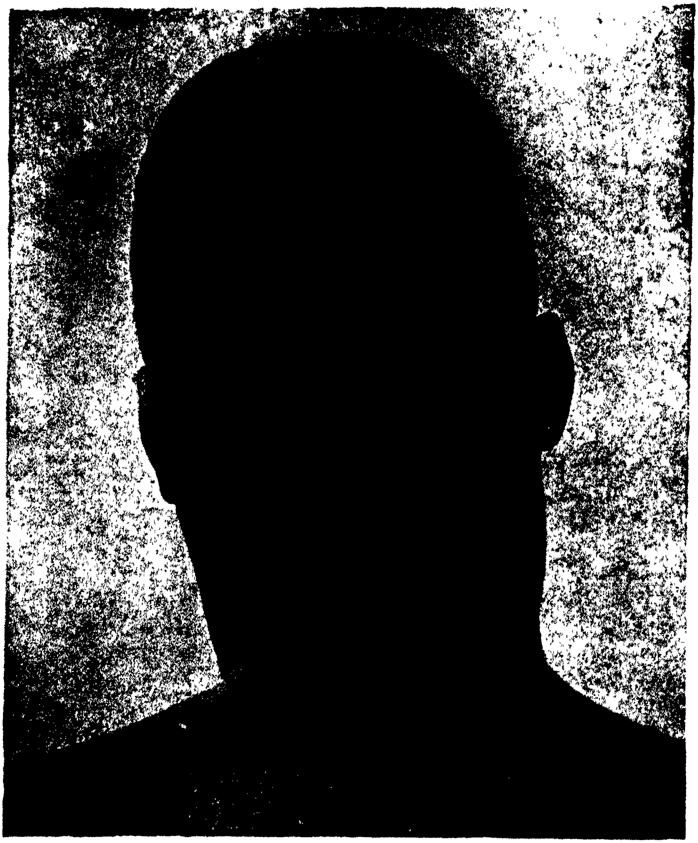


Fig. 16.—Enlargement of cervical lymph-glands in trypanosomiasis (Winterbottom's sign). (*Dr. F. K. Kleine.*)

patients become debilitated, anæmic and feeble, both intellectually and physically. The spleen is usually enlarged. Severe temporal headache is very often present. The heart's action is generally rapid and easily excited, and persistent tachycardia affords an excellent index to persistent infection. The cervical glands and those of other parts of the body enlarge and may become tender. Only one gland may be visibly involved, or there may be polyadenitis, including the abdominal group. The implicated glands may be very prominent, or not easily felt, but are usually most conspicuous in the posterior triangle of the neck (Winterbottom's sign) (Fig. 16). In the early stage of the infection they are soft, later indurated; sometimes they are painless, sometimes distinctly painful and tender, rarely suppurating. This condition of irregular fever, of debility, of polyadenitis, of slight anæmia, may go on for months, or even, in some instances, for years. At this stage there is usually insomnia and lack of concentration.

A proportion of cases may then terminate. Since this disease undergoes at various stages periods of quiescence, which may be very prolonged, it would be rash to call any instance of apparent recovery a radical cure. But experiments and observations by Laveran and others in other forms of trypanosome infection, as well as some cases in Europeans which have come under the Editor's notice, justify the belief that occasionally the parasite does die out spontaneously.

In a given area and in a given population there is a tendency for the virulence of the local trypanosome to decrease with lapse of time. Thus, the trypanosome of the Gold Coast and Southern Nigeria, where sleeping-sickness presumably has long been endemic, is less virulent and much more amenable to treatment than that of Uganda, where it is of recent introduction; indeed the Editor, together with Cooke and Gregg, has described a series of particularly mild cases in Europeans from the Gold Coast in which trypanosomes were discovered during the course of routine blood examination, but which otherwise appeared normal, though one had a circular erythematous patch on the shoulder. Similar instances have been recorded by Lamborn, Howat, Davy, Sicé, Rolin and Mercier.

Remarkable features of human as well as of animal trypanosomiasis are skin affections and local œdemas. In many of the lower animals infected by their special trypanosomes, papular and pustular eruptions are common, in addition to fever and physical lethargy; and in man, especially in negroes, an exceedingly itchy papular eruption is frequent. In the European, and possibly in the negro—but in the latter, less evident on account of his colour—extensive skin areas are affected with a fugitive, patchy, frequently annular erythema (Fig. 17 and Plate VII, facing p. 227), usually most evident on the chest and back, but also very often on the face, legs, and elsewhere. This erythema seems to occur most frequently and most distinctly in the earlier stages of the infection. Some of the patches may be six inches or even a foot in diameter, their margins fading off insensibly into the surrounding normal skin. It usually takes the form of large rings, occasionally complete, more frequently interrupted and irregular. Sometimes it is confined to annular rings on the shoulders. Erythema nodosum sometimes occurs also. Pressure or any irritation of the skin gives rise at once to transient congestion from vasomotor paralysis of the skin capillaries. The rash can be brought out by heat, and especially by hot baths. Xeroderma and pruritus are often present in the terminal stages.

In some of the lower animals a usual feature is œdema of certain parts of the body, especially of the eyelids, the sheath of the penis, the under-surface of the abdomen, and the neck. Similar, though less extensive, œdemas occur in man, in whom they are most apparent in the face and about the site of the erythema. In many instances there is a general fullness of the features which, with concomitant flushing, is apt to convey a false impression of sound health.

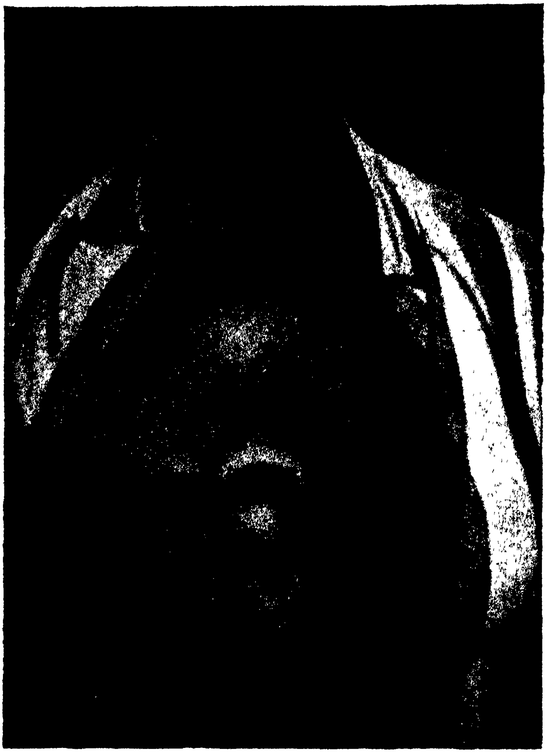


Fig. 17.—Rash of human trypanosomiasis. (*Photo by R. McKay.*)

Neuralgic pains, cramps, formication, and paræsthesiæ of different kinds are not uncommon. Two of Manson's cases showed recurring orchitis, accompanied by an increase of parasites in the blood. Painful local inflammatory swellings, which after a time subside without suppuration, have been seen in some cases ; periostitis of tibiæ more rarely. Toxic iridocyclitis and choroiditis and deep œdema of the lower eyelid are sometimes met. The eye symptoms are not so evident in man as in the lower animals, interstitial keratitis in infected dogs being comparatively frequent.

In most cases the spleen is enlarged, sometimes enormously, fluctuating with the fever, in the absence of concomitant malaria which, however, is a not infrequent complication. The liver may be similarly affected.

Although trypanosome infection is not, as a rule, transmitted to the fœtus, the abortion-rate is increased from the normal 7 per cent. in Congo natives to 81·7 per cent., and the infant mortality-rate from 29 per cent. to 50 per cent. Trypanosomiasis in infants is extremely rare, though Kellersberger has recorded infection in one three weeks old (*see* p. 119).

Death from intercurrent disease, from rapidly developing cerebral implication causing convulsions, status epilepticus or coma may supervene at any stage of trypanosomiasis. Usually the case gradually drifts into the stage known as "sleeping-sickness." It is usually believed that the development of the sleeping-sickness stage in trypanosomiasis concurs with and depends on the entry of the parasite into the cerebro-spinal canal.

Sleeping-sickness stage (cerebral trypanosomiasis).—The terminal stage of trypanosome infection sometimes exhibits acute features, and sometimes is exceedingly chronic. While an interval of several years, possibly eight, may elapse from the commencement of the infection to the development of this terminal stage (Rodhain), in the majority of cases the progress is much more rapid. The characteristic terminal symptoms depend on implication of the nervous system, either by the parasite itself or by its toxins.

The average duration of this stage in the African is from four to eight months, not infrequently less; very chronic cases with a course of more than a year are rare. Some observers refer to cases running on for three years or even longer, with occasional temporary ameliorations.

Generally, the first indications of the oncoming of sleeping-sickness are merely an accentuation of the debility and languor usually associated with trypanosome infection. There is disinclination to exertion; slow, shuffling gait; morose, vacant expression; relaxation of features; hanging of the lower lip; puffiness and drooping of the eyelids; tendency to lapse into sleep or a condition simulating sleep, somnolence during the day-time contrasting with restlessness at night; slowness in answering questions; shirking of the day's task. Dull headache is generally present. Later, there may be fibrillary twitching of muscles, especially of the tongue, and tremor of the hands more rarely of the legs, indicating involvement of the motor centres. By this time the patient has taken to bed, or he lies about in a corner of his hut, indifferent to everything going on around him, but still able to speak and take food if brought to him. He never spontaneously engages in conversation, or even asks for food. As torpor deepens he forgets even to chew his food, falling asleep perhaps in the act of conveying it to his mouth, or with the half-masticated bolus still in his cheek. Nevertheless, such food as he can be persuaded to take is digested and assimilated. Consequently, if he is properly nursed, there may be no general wasting. As time goes on, he begins to lose flesh, tremor of hands and tongue becomes more marked, and convulsive or choreic movements may occur in the limbs or in limited muscular areas. (Fig. 18.) Sometimes these convulsions are followed by local temporary paralysis. Sometimes, too, rigidity of the cervical muscles and retraction of the head occur. There is usually an intolerable pruritus of the skin; bedsores tend to form; the lips become swollen, and the saliva dribbles from the mouth. Gradually the lethargy deepens; the body wastes; the bedsores extend; the sphincters relax; and finally the patient dies comatose, or sinks from slowly advancing asthenia. Possibly he succumbs to convulsions, hyperpyrexia, pneumonia, dysentery or other intercurrent condition.

The manifestations described are subject to considerable variations. Thus, mania is not uncommon; delusions may present themselves, or psychical and physical symptoms not unlike those of general paralysis of the insane are developed. In the European, death is frequently due to convulsions, probably from the presence of the trypanosomes in the brain. Deep hyperæsthesia of the muscles is also quite common. The habits usually become bestial.

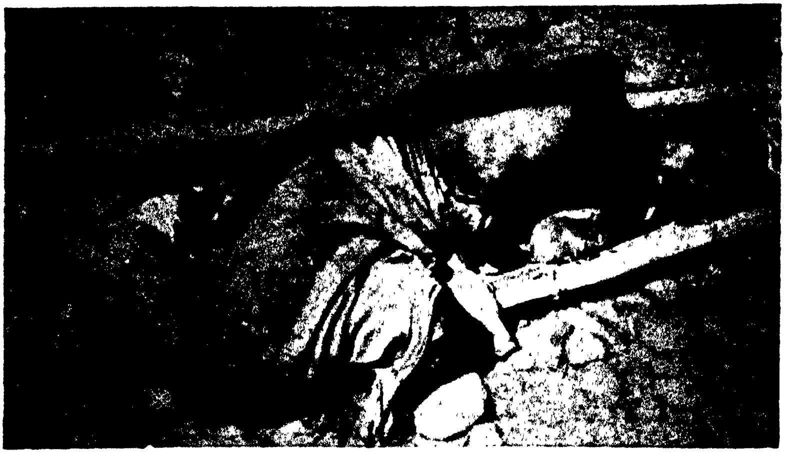


Fig. 18.—Cerebral trypanosomiasis. Appearance of patient in last stages of the disease. (*Dr. F. K. Kleine.*)

During the whole course of the nervous stage of trypanosomiasis the other symptoms already described as characteristic of the infection may be in evidence. The knee-jerks, though lost towards the end, are active at first; the fundus oculi is usually normal; the sphincters, until towards the end, are controlled; the urine is normal, and the bowels, although generally tending to constipation, act with more or less regularity.

Trypanosomiasis in natives.—Lester recognizes three categories in Nigeria :—

(1) Mild, with few symptoms, when equilibrium has been established between patient and parasite.

(2) Involvement of the central nervous system—the commonest form.

(3) Acute, leading to death before the central nervous system symptoms develop, toxæmia being the salient feature.

Elsewhere the same three types are found, but the acute form predominates, especially in Tanganyika, where *T. rhodesiense* is the common parasite.

In Central African natives symptoms of trypanosomiasis are considerably aggravated by, and in many cases mistaken for, those of other diseases. The patient is almost invariably infected with malaria, ancylostomiasis, bilharziasis, and possibly filariasis, besides which much of the emaciation and the specific complications—septic rhinitis, otitis—are due to starvation and neglect.

Mortality.—Although spontaneous recovery may take place in the early stages of trypanosomiasis, it is believed that when the disease has arrived at the stage of sleeping-sickness, death is inevitable. Corré has told how native villages in Senegambia have been depopulated. What has occurred on the Congo, in Angola, and in Uganda, bears out this estimate of the gravity of the disease in epidemic form. Many islands in the Victoria Nyanza have been completely depopulated. The population of the implicated districts of Uganda, originally about 300,000, was reduced in six years to 100,000 by sleeping-sickness.

Immunity.—Man is immune to infection with the commoner trypanosomes of big game, *T. congolense* and *T. vivax*, and certain mammals are immune to trypanosomes which are pathogenic to others. Thus, *T. vivax* is pathogenic to horses and cattle, whilst rabbits, guinea-pigs, and mice are refractory. Although there is no direct evidence that man becomes immune after exposure to infection with *T. gambiense*, yet there is no doubt that when the disease has lasted any length of time in a district, as in Southern Nigeria, the inhabitants exhibit a degree of resistance not seen in districts more recently invaded.

The non-immune European generally suffers in a more acute form than does the Central African native under similar conditions. Russell and others who have studied the phenomena of immunity in man believe that the course of an infection with a pathogenic trypanosome depends upon the capacity of that organism to vary in a serological sense so often that it defeats possible variations in the host's defence.

Trypanocidal action of human serum on trypanosomes.—Following the interesting discovery by Laveran, in 1902, that normal human serum exerts a marked effect on the course of trypanosome infection in animals, a large amount of work has been devoted to this subject with the object of discovering an effective trypanocidal serum. Yorke, Adams and Murgatroyd have shown that normal human serum exerts a pronounced trypanocidal action *in vitro* at 37° C. on a number of strains of pathogenic trypanosomes, even when the serum is diluted 5,000–25,000 times; but in certain pathological conditions of the liver this power is lost entirely *in vitro*. The interesting fact has been observed that in the sera of certain normal sheep and rabbits, an active trypanocidal substance exists which, when mixed with normal human serum, inhibits the trypanocidal action of the latter. A curious and almost inexplicable feature is the fact that *T. rhodesiense*, *T. equiperdum* and *T. congolense* are rapidly destroyed *in vitro* by this method, but *T. gambiense* is apparently unharmed. Possibly in this observation lies the explanation of man's immunity to infection with the pathogenic trypanosomes of cattle and other stock.

Diagnosis.—Chronic irregular fever, more especially if associated with enlarged cervical glands and, in the European, erythema multiforme, in a patient who has resided in tropical Africa at any time during the previous seven years, but especially recently, suggests a tentative diagnosis of trypanosomiasis and detailed examination with this possibility in view. Diseases with which trypanosomiasis might be confounded are malaria, kala-azar, pellagra, syphilis, leprosy, lymphadenoma (Pel-Ebstein disease), and, in its later stages, beriberi.

The diagnosis of trypanosomiasis is made absolute by blood examination, but the serum-formalin reaction (*see* p. 163) is usually positive in well-established cases and therefore may serve as a rough guide for differentiation from other African fevers on a large scale (Hope-Gill, Morrison and Dye). Sicé and his collaborators have shown that there is a considerable diminution in the total serum proteins, and the loss is mainly due to decrease in serum albumin. The ratio of serum albumin to globulin is always less than it is in normal persons. Davis, Brown and Brown (*see* p. 206) have recently worked out a specific immunity reaction in trypanosomiasis known as the "adhesion phenomenon." This reaction is characterized by adhesion of blood platelets and cells to the parasite when acted upon by immune plasma *in vitro*. For this purpose trypanosomes, immune serum, complement and human cells are incubated together; if the serum is homologous the red cells become firmly adherent to the trypanosomes. Standard concentrations of red cells and trypanosomes are necessary to obtain constant results. Agglomeration and trypanolysis may take place, even if the red cells are unsuitable as indicators. This reaction is said to be specific for different species of trypanosome, and the immune body exhibits a high degree of thermostability. The test can be used in recognizing species of wild game which may act as reservoirs of *T. gambiense*.

Microscopical diagnosis of trypanosomiasis is sometimes difficult. Anæmia, as well as a relative increase of large mononuclear leucocytes, usually occurs. A well-stained blood preparation exhibits, even to the naked eye, a remarkable clumping of the red corpuscles (auto-agglutination). As a rule, the parasites in the peripheral circulation are few, many fields having to be hunted before one is discovered. Sometimes none can be found; rarely are they abundant, as in the acute forms of *T. rhodesiense*. The thick-drop method should always be employed.

Centrifuging citrated blood may prove of considerable assistance. Broden used 9 c.c. of blood to 1 c.c. of 6 per cent. citrate solution, centrifuged at first at 1,000 and subsequently at 1,500 revolutions for 10 minutes. The supernatant fluid of the latter is again centrifuged at 2,000 revolutions for 20 minutes, when the trypanosomes will be found in the precipitate. Letonturier, Tanon and Jamot consider that this triple centrifugation method gives 92 per cent. of positive results. Blood or lymph gland cultures on Razgha's medium have given satisfactory results. (*See* p. 1017.)

Dutton and Todd emphasized the value of *lymph-gland puncture* and examination of the aspirated lymph as the most certain method, particularly in the earlier stages of the disease, when the glands are soft before they have become sclerosed, and the trypanosomes abound in the lymph. This method succeeds in 87·7 per cent. of cases. An ordinary hypodermic syringe suffices to aspirate a sufficiency of lymph, of which films are prepared and stained in the ordinary way (*see* p. 162). Massage of the gland assists the flow of lymph into the lumen of the needle. Gland-puncture should always be reinforced by the examination of thick blood-films. The glands may be unilateral or bilateral; sometimes they reach the size of a pigeon's egg and every gradation may be shown. Although the superficial glands may be easy to palpate, deeper ones may be more difficult. Three procedures for palpation are necessary: deep palpation, superficial palpation, and palpation by passing the palmar surface of the hand over the neck. The glands should have the consistency of a ripe plum.

In the Belgian Congo (Foréami system) gland palpation is systematically performed by the European staff; microscopic examination of gland juice and blood by specially trained native assistants.

Cerebro-spinal fluid, obtained by lumbar puncture and centrifuged, affords another (though not always a practicable) means of finding the parasite; according to Broden, parasites may be demonstrated in this manner in 4·5 per cent. of cases, but if the trypanosome is not found, suggestive information may be obtained from a lymphocyte-cell count of the fluid, as this may be increased to over 1,000 per c.mm. The globulin content of the fluid is also increased, but the colloidal gold curve is of the paretic type. The presence of the morula cell of Mott is diagnostic.

The importance of puncture of the cerebello-medullary space in the diagnosis was emphasized by Tajera. Suboccipital puncture through the occipito-atlantoid ligament into the *cisterna cerebello-medullaris* is simple and practically devoid of risk.

Le Port stated that the early changes in the choroidal plexus in trypanosomiasis are confined to the fourth ventricle, so that the immediate consequence is an interruption of the connections between the ventricles and the subarachnoid space. The only real orifices by which these two centres intercommunicate are by the foramina of Luschka, which lie between the cerebellar peduncles in the lateral angles of the fourth ventricle. These orifices are covered by the lateral choroidal plexuses of the ventricle. Obstruction of the foramina of Luschka results in separation of the subarachnoid space from the ventricles where the cerebro-spinal fluid is produced, and this causes automatically a state of disequilibrium of tension of the fluid between the two cavities. The intraventricular tension thus produced may give rise to a syndrome which is responsible for the signs of the first stage of sleeping-sickness. Intraventricular hypertension manifests itself by headache, nausea and a degree of somnolence.

Sicé has proved that the earliest reaction resulting from meningeal lesions is cellular; at first it is slight and unaccompanied by clinical signs; usually it progresses slowly, and the intensity of the meningeal lesions is shown by the number and character of the cells. The presence of leucocytes indicates that the lesions are active and, probably, recent. Plasma cells, dead cells and morula cells (Mott) indicate older and more chronic lesions. As the cellular reaction develops, so the albumin content gradually increases. Prognosis can therefore be based upon the amount of albumin in the spinal fluid. Though this can be estimated by a number of different techniques, the proportion of the albumin and the globulin in the cerebro-spinal fluid is considered by most authorities to run parallel with the number of cells present.

Animal inoculation is used if the parasite is not found by blood or lymph examination, 2–10 c.c. of the blood being drawn from a vein and injected. Of the ordinary laboratory animals, the most susceptible, and therefore most reliable, are the guinea-pig, the rat, the dog, and *Macaca* and *Cercopithecus* monkeys. Such inoculations are of value as a test of recovery, as well as for diagnosis.

The intraperitoneal injection of olive oil in experimental animals aids in establishing the infection in cases where the parasites are scanty (Saunders).

Sternal puncture has recently been introduced as a reliable and ready method of diagnosis. Guibert and Boscq found *T. gambiense* in the bone marrow of 29 out of 30 untreated cases, whilst Jospin and Gallais claim that it is superior to any other method.

The trypanosome is easily stained by most dyes, those in use for malaria work giving the best results. A ⅙-in. objective suffices to find the parasite.

Differential diagnosis.—Kala-azar and trypanosomiasis, especially in their earlier stages, may be difficult to differentiate, but enlarged glands, local œdema and erythema multiforme in trypanosomiasis, and their absence in kala-azar, suffice for distinction. Blood or gland-lymph examination, or, if this be negative, hepatic or splenic puncture, should establish the diagnosis.

General paralysis of the insane, cerebral tumour, forms of meningitis, especially encephalitis lethargica (often inaptly termed " sleepy sickness "), have features in common with trypanosomiasis and must be considered. The serum of some cases of trypanosomiasis has been said to give a positive Wassermann reaction, but this may be due to a co-existing syphilitic infection.

TREATMENT

Especially in natives, preliminary treatment directed towards eliminating superimposed infections with ancylostomes or bilharzia is advisable, on account of damage to the liver-cells which renders toleration of arsenical drugs difficult.

1. Treatment with Antrypol.—" Bayer 205 " (urea of acid dimeta-aminobenzoyl - meta - aminoparamethylbenzoyl - 1 - naphthylamino - 4-6-8 trisulphonate of soda) (*Germanin, Antrypol,*[1] *Belganyl, Moranyl, Suramin*) originally introduced in 1920, has been of great value in eradicating infection, especially during the earlier stages.

In animals infected with trypanosomes, antrypol has been found to be remarkably non-toxic, and the *dosis tolerata* has been estimated to be 160 times that of the *dosis therapeutica,* when injected intramuscularly or intravenously. It is lethal to *Trypanosoma brucei, T. gambiense* and *T. rhodesiense* ; moreover, it has been found to exert a definite prophylactic action. The average dose for man is 1 grm. dissolved in 10 c.c. of distilled water (or a 10 per cent. solution) injected intravenously. The total amount to effect a cure is about 10 grm., though the trypanosomes usually disappear and are not usually found again after 5 grm. As a rule, trypanosomes vanish twelve hours after the first injection. It is customary to repeat the dose at weekly intervals.

---

[1] The preparation used in veterinary practice is known as " Naganol."

In an early infection, directly the disease has been diagnosed, the best and most lasting results are obtained by giving bigger initial doses, such as 1 grm. on the first, third, tenth, and thirteenth days. In exceptional circumstances individual doses of 1·5–2 grm. can be given.

It is thought that the value of antrypol lies in its power of rendering trypanosomes fit for phagocytosis by the reticulo-endothelial cells—a kind of opsonizing effect. This action greatly enhances the effect in the living animal and thus explains its greater efficiency *in vivo* than *in vitro*.

There are some reasons for believing that its delayed action is due to combination with plasma and tissue proteins, so that the serum, cerebrospinal fluid and urine continue subsequently to exhibit trypanocidal action when injected into trypanosome-infected mice.

Immediately after the injection of the drug, both the physical condition and mental outlook of the patient are improved. The drug is harmless to man, except that it has a cumulative action and is a kidney irritant, so that, after three or four injections, the urine contains albumin and small yellow, granular casts. This is the result of excretion *via* the urinary tubules, and lasts about six weeks. In some susceptible individuals toxic dermatitis—a red, itching and papular rash—develops, usually after the third injection. According to Corson, a painful condition of the feet, apparently peripheral neuritis, has sometimes been observed.

Intrathecal injection of antrypol cannot be recommended, as pain, vomiting, headache, convulsions and twitchings may ensue after small doses, and advanced cases derive no benefit. Although it is now recognized to be the most active substance in the treatment of sleeping-sickness and has cured cases where all other forms of treatment have failed, yet it appears incapable of destroying trypanosomes when once they have entered the grey matter of the brain. Kleine and Fischer originally reported on the treatment of 185 cases of *T. gambiense* infection in Africa, of which 80 per cent. showed a marked clinical improvement and were considered cured. Since that time many series of cases have been published which bear out the original claims. Thus, Dye, in Nyasaland, reported favourably on the doses usually advocated, while Mayer (1928) published a critical review of the subject. The Editor has investigated three cases in Europeans in whom a permanent cure was effected with a total of 3–5 grm. of antrypol.

2. Treatment with tryparsamide.—*Tryparsamide* (sodium salt of N-phenylglycineamide-*p*-arsonate) was originally introduced for the treatment of trypanosomiasis by W. H. Brown and Louise Pearce, of the Rockefeller Institute. (The French equivalent, " Fourneau 270 " (Orsanine) is acetyl-*p*-amino-*o*-oxyphenyl arsenic acid, and has been used extensively in French Equatorial Africa.) Tryparsamide should contain not less than 25·1 per cent. of arsenic.

When injected into the tissues it is quickly absorbed; it may be given by either the intramuscular or the intravenous route. The chemotherapeutic index of tryparsamide, i.e., the ratio between the curative dose and the maximum tolerated dose, is 1 : 2; for atoxyl it is 1 : 1. The individual doses are large, varying from 1 to 4 grm.; the optimum is about 83 mgm. per kilogram of body-weight. The drug has a marked effect on the symptoms, especially when the nervous system is involved; its chief value is the ease with which it penetrates into the cerebro-spinal fluid and eliminates the trypanosomes. Furthermore, there is great reduction of lymphocytes in this fluid in cerebral trypanosomiasis, which is attributed to its high power of penetration. In an average case the initial dose should be 1 grm. in 10 c.c. of distilled water: subsequently it may be given in 2 grm. doses, three times weekly. A total dosage of 24 grm. is, as a rule, necessary.

Van den Branden considers 70–80 grm. necessary to obtain permanent benefit in chronic cases. In the mildest cases he was able to obtain 57 per cent. apparent cures with a total of between 20–60 grm., but 71·6 per cent. only when trypanosomes were present in the cerebro-spinal fluid.

According to Chesterman, who has had a large experience of tryparsamide the intravenous route is the most effective; the solution should not exceed 40 per cent., which is about saturation point. Care should be taken to see that the water is not alkaline, as this produces precipitation. Intramuscular injection is also efficacious, but in this case the solution should not be stronger than 20 per cent. Experience has proved that it is not possible to procure "*therapia sterilisans magna*," as prolonged administration of the maximum tolerated dose gives the best results.

Children up to twelve years of age tolerate the drug well and may be given doses up to 80 mgm. per Kg. of body-weight for twelve injections.

In more *advanced cases* in adults smaller doses up to 20 mgm. per Kg. of body-weight should be given, on the fourth day 30 mgm. per Kg., and on the eighth a course of 20 injections of 40 mgm. per Kg. at four-day intervals should be commenced. A course of ten injections should be repeated three months after the first. If the drug is used in strengths of more than 20 per cent. by the intramuscular route, induration or abscesses may ensure. Herxheimer reactions with acute mania have been noted when initial doses are excessive.

Physical improvement and restoration of mental activity, together with normal cell count and albumin content of the cerebro-spinal fluid for a period of one year, should be considered evidence of cure. Excess of albumin and increase of cells in the cerebro-spinal fluid is sometimes noted for a short period, but may be merely temporary.

Optic neuritis.—Some patients are sensitive to tryparsamide. Optic neuritis is apt to develop in patients, previously treated with small quantities, to whom a second course is given. There appears to be no agreement on the amount of tryparsamide which provokes optic neuritis. The Editor has seen two cases where blindness ensued after 13 grm. Lauterburg has reported a series in which blindness occurred in 7·4 per cent.; all had received weekly doses of 2 to 3 grm. Advanced cases are much more likely to develop visual troubles than early ones, and therefore must be treated with caution. Objective signs of eye damage are not manifest early enough to make it possible to prevent complete blindness, but the fundus remains normal for a long time and pallor of the disc becomes apparent quite late; a dangerous sign is narrowing of the fields of vision. Jamot reports that out of 25,638 patients treated with tryparsamide, 233 developed ocular trouble; in 30 there was amblyopia and in 17 amaurosis. Casten, in his studies of treatment of cerebral syphilis with tryparsamide, has not found the same amount of visual trouble. He classifies the ocular symptoms into (*a*) subjective, with blurring of vision, and (*b*) objective, with ocular damage. The first state comes on 15 to 30 hours after administration and lasts from one to three weeks; it always clears up on cessation of treatment:

the second becomes permanent, with diminution of visual fields, and may lead to optic atrophy.

Premonitory symptoms may be photophobia, lacrimation, ocular pain and dimness of vision. It should be made the rule to test the vision of each patient before injection by detection of some small object. In any suspicious case administration of arsenicals should be suspended and tartar emetic substituted. It must be remembered that the action of arsenic is often delayed and symptoms of optic neuritis may progress, even after cessation of treatment. This was the case when atoxyl was commonly employed in treatment of trypanosomiasis.

Results of treatment with tryparsamide.—In early cases apparent cure is almost invariable, but tryparsamide acts less certainly after previous administration of atoxyl or other arsenicals. In more advanced cases figures vary, but, given good conditions, in the absence of other debilitating diseases, when degeneration of the central nervous system has not progressed too far and when the cerebrospinal fluid does not contain too many cells, this drug gives gratifying results.

Tartar emetic, which is curative in some forms of cattle trypanosomiasis, is now mostly used to reinforce tryparsamide treatment in cases complicated by bilharziasis.

Other arsenical compounds.—Van den Branden has reported on a trial of *etharsanol* (monosodium salt of 2-*p*-arsono-arsilino-ethanol) and *proparsonal* (monosodium salt of 3-*p*-arsono-anilino-proponol), containing 20 per cent. of arsenic. These were injected in doses of 2 grm. and their action was found to be comparable to that of tryparsamide, but both appear to produce optical disturbances more readily.

Yorke, Murgatroyd, Glyn-Hughes and Ross find that sodium succinanilomethylamide-*p*-arsonate (*neocryl*) compares favourably with tryparsamide in being less toxic and possessing a somewhat greater trypanocidal activity. The doses are similar to those of tryparsamide, but ultimate results are stated by Acres to be less favourable in the second stage of trypanosomiasis.

N-phenylglycineamide-p-arsonic acid, of which tryparsamide is the sodium salt, may be given by the mouth, which, in dealing with large numbers of natives, is simpler. In contrast to tryparsamide it is well tolerated by this route and causes disappearance of trypanosomes from the blood and cerebrospinal fluid, though in a slower and less dramatic manner. The tablets (supplied by Messrs. May & Baker) are crushed in water and swallowed. The dosage is twice that of tryparsamide by the parenteral route and has the advantage of being less apt to produce optic neuritis.

Gruhzit, Lindsay, Hendricks and Dodd found *mapharside* satisfactory. It is amino-paraphydroxyphenyl-arsine oxide and is believed to be the compound elaborated in the body after injection of arsphenamine. The initial dose is 40 mgm. per kilogram body-weight for women : 60 mgm. for men. (*See* p. 822.)

3. Synergic or combined treatment with antrypol and tryparsamide.—Comparatively few European cases have been recorded, but in these striking recoveries have been obtained by combining tryparsamide and antrypol therapy. This is borne out by the experimental work of Yorke indicating that pathogenic trypanosomes may become drug-fast, and that resistance (*see* p. 188) is also developed towards antrypol (but more slowly). The Editor recorded 11 Europeans in whom success was obtained by antrypol therapy in tryparsamide-resistant cases and *vice versa*. The conclusion which can be drawn from clinical experience is that, when once a clinical and parasitological relapse has taken place after an initial course of treatment with one trypanocidal drug, it is unwise to persist with larger doses, but a change should be made to remedies of entirely different chemical constitution. In the Editor's opinion, preliminary antrypol treatment in maximum tolerated doses should be followed by tryparsamide injections in moderate doses—2 grm. twice weekly (or 4 grm. per week). Chesterman advocates two or three large doses of antrypol (3 doses of 1·5 grm. for an adult at three- or four-day intervals) followed by 6–8 weekly injections of medium doses of tryparsamide, i.e., 70 mgm. per kilo. body-weight for children; 55 mgm. per kilo. for adolescents; and 45 mgm. per kilo. for adults.

Between these two courses a rest of ten to fourteen days should be permitted, until the urine becomes free from albumin, before the administration of tryparsamide. Alternating injections of tryparsamide and antrypol, with intervals of three days, have also been given with good effect. This method was used by Maclean in Tanganyika, Duke in Uganda, and Dye in Nyasaland, and is now the standard method adopted by the Foréami organization in the Belgian Congo.

Sicé and Torresi, who favour synergic medication, found that the best combinations are of antrypol and tryparsamide, antrypol and anthiomaline, tartar emetic and treponyl.

Other preparations.—Lourie, Yorke and Browning announced that *synthalin*—a guanidine compound—exerts a trypanocidal action. An allied substance, *undecane diamidine*, is also effective.

Diamidino stilbene (*stilbamidine*) (*see also* p. 166), with therapeutic index of 30, was found to have considerable activity in experimental trypanosomiasis, and was tried out in Nigeria and Gambia by Harding and Bowesman. Intravenous injections sometimes give rise to temporary symptoms, but it may also be administered by the intramuscular route. This drug causes amelioration of clinical signs and symptoms, though it is unsuited for cases in which the protein content of the cerebro-spinal fluid is above 0·05 per cent. This treatment takes about half the time necessary for a full course of tryparsamide, and is promising.

Pentamidine (4·4 diaminodiphenoxypentone) was tried on a limited scale by Lawson (1942) and Gilbert (1943) in Uganda and Northern Rhodesia. It was given daily for 18 days intramuscularly in doses varying from 1·6 to 5·15 mgm. per kilo. It certainly reduced the cell-count of the cerebro-spinal fluid. At least 2 mgm. per kilo should be given, preferably intravenously.[1]

General considerations.—The exact manner in which the trypanocidal drugs act is a problem which has not been satisfactorily settled. One aspect of the question is drug-resistance. Van Hoof, Henrard and Peel found natural drug-resistance of *T. gambiense* to tryparsamide much commoner than is generally believed. It appears that a trypanosome can suddenly acquire a certain degree of arsenic-resistance by passage through unaccustomed hosts. Murgatroyd, Russell and Yorke considered that trivalent arsenical compounds owe their therapeutic activity to the fact that their trypanocidal substances circulate unchanged in the blood-stream, and that tryparsamide owes its curative power to the fact that it is gradually reduced in the blood, possibly also in the tissues, into a corresponding trivalent compound. It escapes from the blood with remarkable speed, and consequently the fact that the trypanocidal titre of the blood following injections of tryparsamide never rises beyond modest limits can be explained on the ground that, as fast as the tryparsamide is reduced to its trivalent form, it is eliminated from the blood.

---

[1] Successful treatment of a European case is reported (1944) by Bomford. A total of 4·3 grm. of pentamidine was injected in 39 days, in 20 treatments, in doses from 100–300 mgm., mostly on successive days. On the other hand, McComas and Martin (1944) had a fatality in an African after the third injection of 100 mgm., death being due to a Herxheimer reaction.

Prophylaxis.—Indications for prophylaxis are based principally on the habits of *Glossina palpalis* and *G. tachinoides*, and on the conditions of infection (Plate V, facing p. 121).

In endemic regions fly areas should be located and avoided. If such regions have to be traversed, the journey should be made during dark nights, when tsetse flies do not feed, or with such precautions as are used by the natives for the protection of their cattle in nagana-infected spots. Those who are forced to live in tsetse regions should have their houses and persons carefully guarded against the fly. Manifestly, it is desirable—whether it is feasible is another question—to avoid localities in which the natives are affected, and to prevent infection of the local tsetse flies by those who have trypanosomes in their blood, either by means of mosquito-netting, or by evacuating the population from the usually very limited fly area to some neighbouring fly-free spot. Movement of infected individuals to hitherto uninfected countries must necessarily be attended with great risk of the introduction of the disease. Whether such movement can be prevented in primitive lands depends greatly on local circumstances. Some easily recognized condition, more or less general in trypanosomiasis—viz., enlargement of the cervical glands—should be employed in eliminating dangerous individuals. Many years ago slave-dealers adopted this method to shield themselves from loss. As a rough test it has some value. But in some cases of trypanosomiasis these glands are not appreciably enlarged at all times. Moreover, as they are often enlarged in other conditions, injustice might be done.

The fly ground proper is always a very narrow strip, not more than ten to fifteen yards wide, along the water's edge. The insects very rarely extend their feeding beat sixty yards beyond this, whether on the land or on the water side. It is true they may follow with great persistency a man who has just passed through this narrow belt, for several hundred yards, rarely for half a mile; but it is obvious that if the ten or fifteen yards at the water's edge be made unsuitable for the fly, as can be done by clearing it of jungle, there will soon be no flies to follow human beings, and the place will become safe. Therefore, where feasible, fly spots, where there are landing-places, ferries, wells, or roads, should either be avoided altogether or be cleared of jungle for some yards—to be safe, thirty—from the water's edge. This is a practicable measure of proved value in Uganda.

Fly traps.—Harris has had very considerable success with a tsetse-fly trap of his own devising, the materials for each costing about 30s. The trap, which is designed to resemble a cow or antelope, consists of a framework of light wood, covered by hessian cloth, roughly triangular in section, with a flat top, 6 ft. long by 3 ft. wide, the sides converging to about 3 in. apart with a narrow open slit along the bottom, the ends being vertical and triangular. The body is hung on wires so that the open slit is 48 in. from the ground. To the flat upper surface a transparent cage of wire gauze, of a mesh sufficient to retain a fly, is fixed; where the cage fits to the flat surface the cloth is removed and the wire so arranged that the flies cannot return to the hollow body of the trap. These traps are suspended on the sunny margins of evergreen bush haunts of the flies, and so placed that they throw a separate shadow, and it has been found that, in suitable weather, each trap will kill 100 to 200 flies daily. This trap has been specially successful in catching large numbers of *Glossina pallidipes* and *G. palpalis*, but is not so successful with *G. morsitans*.

Swynnerton employed a similar trap containing a live calf to which the flies are attracted by scent. The most effective is a moving screen carried by fly-boys, who are able to catch with a net practically every fly that the screen attracts. *Glossina pallidipes* and *G. palpalis* can readily be caught by any suitable trap, but other species (*G. morsitans* and *G. swynnertoni*) are less responsive. Considerable care is required in the siting and setting of traps, which should be placed as conspicuously as possible.

Drug prophylaxis.—Van Hoof reported that by systematic injection of infected natives with tryparsamide a progressive lowering of the index of new infections is taking place in the Belgian Congo; but that a constant watch is necessary to maintain this reduction. If vigilance is relaxed, the disease may flare up again with the intensity of an epidemic.

Chemoprophylaxis.—With the advent of antrypol it was hoped that an efficient prophylactic under natural conditions had been procured. So far this method has not given very encouraging results; although a prophylactic injection does not prevent actual infection, it does, according to Kleine, definitely mitigate the pathogenicity of the infecting trypanosome. Fourché, on the Congo, considered that the intravenous injection of 1 grm. in adults, and 0·3 to 0·75 grm. in children and adolescents, had a definite prophylactic value for seven months. Van den Branden inoculated all the inhabitants of a village in the Belgian Congo with the following doses: adults 1 grm.; adolescents 0·5 grm.; children 0·25 grm.; and infants 0·18 grm.—each receiving two injections. At a subsequent visit to this area six months or more afterwards, only one case was found to have developed. Duke's statistics on the chemoprophylactic treatment of Europeans and natives of Uganda with injections of antrypol seemed to indicate that the prophylactic action may last for at least three months, possibly longer. Olovitch (1937) reported very favourably on the mass injection, or "moranylization," of the native population on the Belgian Congo.

Drug-resistance and its transmission through the tsetse.—An important bearing on prophylaxis of trypanosomiasis has been opened up by the work of Yorke and his collaborators on drug-resistance, showing that trypanosomes readily become drug-fast, especially to the arsenic compounds, such as atoxyl, arsacetin and tryparsamide, but less easily to antimony, and that the reaction develops very quickly, within a period of 4–8 weeks. They have proved an even more important and far-reaching fact—that strains of trypanosomes possessing a high degree of resistance to the aromatic arsenicals are transmissible by glossina (*transmission of an acquired character*) and, moreover, that this acquired character of drug-resistance remains unimpaired after two successive passages through the fly.

Other prophylactic measures.—Brilliant results have attended the efforts of the Portuguese to combat sleeping-sickness in the island of Principe, where the annual mortality from the disease amounted to 83 per thousand of the population, and the local industry (cocoa) was threatened with extinction. Besides jungle-clearing, drainage, blood examinations, segregation of the infected, and destruction of possible animal reservoirs of the trypanosome, coolies, dressed in white and carrying on their backs a dark cloth smeared with birdlime, were sent into the jungle, and every night the flies caught were removed and counted. In three years 470,000 glossinæ were caught. As a consequence of this combination of sanitary measures the fly and the sleeping-sickness were exterminated. Of course, it was only the complete isolation and the limited size of the island that made such a result possible.

Complete scientific prophylaxis can be indicated with certainty only when we have full knowledge (1) of the habits of the tsetse flies and of the reasons for their restriction to very limited and apparently capriciously distributed areas ; (2) of what vertebrates under natural conditions are normally hosts of *T. gambiense* (*see also* Appendix, p. 855).

Biological control.—Attempts by Lamborn to introduce a predatory insect which would destroy the pupæ of glossina have so far met but a moderate success. In 1914 Austen suggested the introduction of the chalcidiid—*Spalangia*—into tracts where *G. morsitans* is a pest. Consequently one species of chalcidiid (*Syntomosphyrum glossinæ*) has been bred in large numbers in the laboratory and distributed over an area of Lake Nyasa of about 42 square miles. In the course of three months it was found that 8·7 per cent. of glossina pupæ were parasitized. Roubaud and Treillard have been carrying out some experiments by infecting *Glossina palpalis* with a cocco-bacillus which is pathogenic for muscidæ.

Removal of infected populations.—It is necessary to realize the seriousness of the problem. Trypanosomiasis has interfered with the development of one-quarter of the African continent. In Uganda by 1900 it was estimated to have exterminated two-thirds of the native population. To preserve the hitherto uninfected from trypanosome infection, the Government transported the entire population of the Sesse Islands and neighbouring shore of Victoria Nyanza to fly-free areas in the interior. It was hoped that, the human source of trypanosome supply being thus denied them, the tsetse flies would cease to be infective. Unfortunately, this hope has been disappointed. Three years after the depopulation of the districts involved, Bruce ascertained that local flies could still convey the disease to laboratory animals. Manifestly, *T. gambiense* can flourish under natural conditions in vertebrates other than man. The reservoir host in this instance was found to be the situtunga antelope (*see* p. 121).

Dispersal of tsetse flies by traffic.—The opening up of Central Africa by motor roads and the development of motor traffic has introduced a new problem in the spread of trypanosomiasis, both *gambiense* and *rhodesiense* infections. Jack has shown the tendency of these flies to follow up moving objects and to settle on the backs of pedestrians and cyclists and under the hoods of motor cars. On pedestrians these flies may be carried 10, on motor cars, 50 miles a day. When the moving object stops, the flies move away and seek shade nearby. It has been found necessary to restrict vehicles (including cycles), leaving fly areas, to fixed routes. At the point of exit notices are placed stating that motorists and cyclists must submit to prescribed measures. Native cyclists are cleansed of flies in special gauze cages. Motors are fumigated with " Flit " and the passengers are groomed with insect-nets.

[For a detailed description of tsetse flies (Plate V), *see* pp. 978–983.]

RHODESIENSE SLEEPING-SICKNESS

The trypanosome found in cases of human sleeping-sickness originating in Rhodesia was at first considered to have certain peculiarities when inoculated into the rat. This fact, together with the greater virulence of the disease both in man and in laboratory animals, and the greater resistance to arsenical treatment, led Stephens and Fantham to separate it as a distinct species under the name of *T. rhodesiense*, in 1910. Later, it was proved that it is transmitted by *Glossina morsitans* (Kinghorn and Yorke), not by *G. palpalis*. *G. swynnertoni* is also an efficient intermediary.

Kleine regarded *T. rhodesiense* as the form taken by *T. gambiense* when introduced into a new area and transmitted by tsetse flies of the *morsitans* group, and as distinct from *T. brucei*; whereas Duke considered *T. rhodesiense* and *T. brucei* the same; whilst Lavier held that *T. gambiense*, *T. rhodesiense* and *T. brucei* are one and the same species. The International Commission on Human Trypanosomiasis concluded that *T. rhodesiense* is merely *T. gambiense* transmitted by a different species of tsetse, viz. *G. morsitans*.

Yorke and his collaborators pointed out that the selective cytolytic action of normal serum on trypanosomes and the resistance of *T. gambiense*, in contradistinction to *T. rhodesiense*, may be the true explanation. By this test, *T. rhodesiense* and *T. brucei* appear to be identical, but the serum resistance of *T. rhodesiense* is not a fixed or stable character, but one which is readily acquired and quickly lost. The fact is that there are no constant differential characters in these two human trypanosomes. The *rhodesiense* type is undoubtedly more virulent than *gambiense*, as the latter has become habituated to man by long residence in his body, whilst the former is a more recent acquisition associated with *G. morsitans*, and usually with big game, especially antelopes.

The modern biological view is that the trypanosomes are members of an intraspecific unit, and that they have originated from *T. brucei*, probably from some antelope strain.

Geographical distribution.—This form of trypanosomiasis occurs in North-Eastern Rhodesia, especially in the Luangwa Valley, about the southernmost limit, 14° S.; throughout Tanganyika Territory; in Portuguese East Africa; in Nyasaland, especially in the region south and west of Lake Nyasa: in fact, its distribution closely corresponds with that of *G. morsitans*. (Map II.) A virulent outbreak at Mwanza, Tanganyika, was transmitted by *G. swynnertoni*.

Ætiology.—In human blood (Fig. 19–*1*, *2*), *T. rhodesiense* is morphologically indistinguishable from *T. gambiense* and *T. brucei*: but if it is passed through the rat or guinea-pig, a small but variable proportion of the parasites, especially the stumpy forms, will be seen to have their nuclei located posteriorly to the kinetoplast—that is to say, at the non-flagellar end of the organism (Fig. 19-*3*, *4*, *5*, *6*). This feature, formerly considered specific, is not now regarded as important, because similar changes are undergone by other trypanosomes.

A good deal of work has been expended in attempting to prove and disprove that *T. rhodesiense* is no other than a strain of *T. brucei* inoculated into man. When injected into rats, *T. brucei* exhibits the same proportion of posterior-nucleated forms as *T. rhodesiense* (Bruce). Taute and his fellow-workers disproved this conclusively by inoculating themselves and 129 native porters with dog's and mule's blood containing *T. brucei*, with a negative result, while rats, dogs and a goat, inoculated with the same blood at the same time, succumbed. These experiments, they claimed, definitely disprove that *T. brucei* is in any way pathogenic to man.

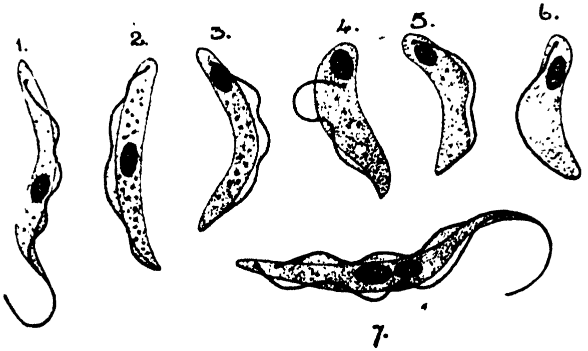


Fig. 19.—Forms of *Trypanosoma rhodesiense*. (*After Laveran.*)
1, 2, Normal forms in blood of man ; 3-6, various stages of posterior displacement of the nucleus ; 7, a dividing form.

Pathology.—The visceral lesions of *T. rhodesiense* trypanosomiasis are probably more often fatal than lesions of the central nervous system. Hawking and Greenfield (1941) described extensive trypanosomal effusions in pleural, peritoneal and pericardial cavities, associated in the latter instance with inflammation of myo-, epi- and endocardium. The cerebrospinal fluid contained numerous trypanosomes, but the lesions in the nervous tissue were singularly slight, being limited to a histiocytic infiltration of the cerebral membranes. The cell count and protein content were not much raised.

Symptoms are similar to those evoked by *T. gambiense*, though febrile paroxysms are more frequent, and severe glandular enlargement is not often met. The disease generally runs a much more rapid course, and fatal symptoms usually supervene within a year of infection, death taking place from convulsions. Acute mental symptoms, such as mania, are frequent.

Buchanan observed that rapid emaciation, weakness, fever and œdema constitute the most obvious signs of toxic action resulting from this infection, while careful observation on the heart showed that in nearly every one there is a marked effect on the cardio-vascular system, with irritability and tachycardia. The characteristic erythematous rash is usually marked.

The course of the infection is usually so rapid that patients succumb before the sleeping-sickness stage develops.

Lamborn and Howat (1985) recorded that very mild and almost symptomless infections may occur in natives of Nyasaland. The parasites are quite numerous in the blood-stream, but are not seen in the glands or cerebro-spinal fluid. On inoculation into animals a virulent infection

Similar cases were reported by Woolf in the valley of the Rovuma

River in Tanganyika in 1910, and it has been shown that these symptomless carriers may be the starting point of an outbreak.

Diagnosis is the same as for *T. gambiense.* In acute cases trypanosomes are plentiful in the peripheral blood and diagnosis can readily be made by examinations of thick drop specimens. Possibly the parasites are more easily demonstrated by lymphatic-gland puncture. Thus, Kleine found, in a series of 32 cases, 24 had trypanosomes in their glands and blood ; 4 in the glands but not in the blood ; and 4 in the blood only.

Corson proved, in a self-inflicted experiment, that a local circular erythema with a darker and slightly tender centre is a useful indication of an infective bite by glossina in light-skinned people.

TREATMENT

Atoxyl, tryparasamide and antimony preparations (*see* pp. 133–135), which are of use in *T. gambiense* infections, appear to be relatively powerless in *T. rhodesiense* cases, but tryparsamide has been used along with antrypol with success (*see* Maclean, p. 136). Unfortunately, some of the apparently cured cases which have been recorded have subsequently relapsed.

The treatment with antrypol (*Germanin*) is more hopeful, and remarkable successes have so far been recorded ; in fact the drug appears to exert a much more immediate action than in *T. gambiense* infections. Dye, in Tanganyika Territory, advised intravenous injections on the first, third and fifth days, and subsequently at intervals of five to seven days till a total of 7 grm. has been administered, and claimed the disappearance of the trypanosomes from the peripheral blood within twenty-four hours. Antrypol, no doubt, has a remarkable sterilizing effect in early hæmic infections.

The Editor had two striking examples in young Europeans, both of whom were permanently cured with 2 grm. of antrypol given within fourteen days from the time the infection was detected : one had entirely failed to respond to tryparsamide. The latter does not exert an action on *T. rhodesiense* comparable to that on *T. gambiense.* Corson, in Tanganyika, believed that tryparsamide has a place in *rhodesiense* infection as an after-treatment.

There is some evidence that in man a strain of antrypol-fast trypanosomes may be evolved, as Morgenroth and Freund demonstrated in mice, and Kleine and Fischer in monkeys and cattle. One case under the Editor's care relapsed and died after 33 grm. of antrypol, and the trypanosomes reappeared in the blood and cerebro-spinal fluid, apparently quite uninfluenced by the drug.

Prophylaxis.—Prompted by his investigations of the hypothesis that big game act as a reservoir for *T. rhodesiense,* Yorke advocated the extermination of this fauna, but recent investigations tend to show that these conclusions were premature and that man himself may often be the chief source of infection. Jack, in Southern Rhodesia, studying the behaviour of *G. morsitans,* found that the fly was attracted to man by stimuli of movement or scent. Dark colours were most attractive, especially black. White clothing appeared to have some protective value.

Other prophylactic measures are the same as those advocated for *T. gambiense.*

Prophylactic injection of antrypol.—Duke (1934) showed by experiments on human volunteers that the prophylactic action of antrypol is more effective against *T. rhodesiense* than *T. gambiense*. He found that a single dose of 1 grm. of antrypol, intravenously, will protect a man for at least 118 days. Within certain undetermined limits the protective effect may be directly proportionate to the number of doses given ; but it is advisable that inoculations should be repeated every three months.

For further details of African trypanosomes, see Appendix, pp. 853-857.

II. SOUTH AMERICAN HUMAN TRYPANOSOMIASIS

Synonym. Chagas' Disease.

Definition.—Usually an acute, more rarely a chronic disease, caused by *Trypanosoma* (*Schizotrypanum*) *cruzi*, and disseminated by certain reduviid bugs. The acute stage of the disease is characterized by diarrhœa and enlargement of lymphatic glands and spleen, accompanied by cerebral symptoms. The chronic form may manifest special symptoms, according as the heart or other important organs are most invaded by the parasite.

History.—Originally the trypanosome was found in the blood of a monkey which had been subjected experimentally to the bites of *Panstrongylus* (*Triatoma*) *megistus*, and subsequently in 1909 Chagas found the same trypanosome in children in Brazil; at the same time he traced the development of *T. cruzi* in the reduviid bug, *Panstrongylus megistus*, which transmits the disease to man and domestic animals, although allied species of bug, and even other arthropods, have been found by Brumpt to have the power of transmitting the infection, at any rate under experimental conditions. The most complete work on this subject is the monograph by Dr. F. L. Nino, Buenos Aires, 1929.

Geographical distribution.—In the provinces of Minas Geraes, São Paulo, Rio Grande do Sul, and Goyaz in Brazil ; in the states of Trujillo and Miranda in Venezuela ; in San Salvador (Segovia) ; and in the Western Argentine in Tucuman and Jujuy (Mühlens and Zuccarini) ; in children in Cordoba (Argentina) and in the Catamarca province (Geoghegan). (Map I.) The disease has also recently been found in Panama and in Guatemala (Reichenow), in Bolivia and Peru (Escomel), Chile (provinces of Tarapacti and Jurico—Gasic), in Venezuela, San Salvador (Tejera), in Uruguay (Talice), and in Mexico (Brumpt and Mazzota).

That this trypanosome is probably a more frequent infection than has hitherto been suspected, is shown by the fact that Noguchi (1924) recorded the isolation of a trypanosome from the blood of a yellow-fever patient in Colombia.

Trypanosoma cruzi, or trypanosomes resembling it, have been found in ugs (*Panstrongylus*, *Triatoma* and *Rhodnius*) in California and in Texas, t they apparently do not transmit the disease to man in these regions.

It remains to be seen whether *T. cruzi* is confined solely to the New World, Malamos has discovered this trypanosome in monkeys imported into Germany m the Dutch East Indies, where *Triatoma rubrofasciata* is known to occur d is infected with a trypanosome (*T. conorrhini*).

It is remarkable, as pointed out by Hoare, what a comparatively rare human disease this is, considering its wide range in the insect inter-m "

Ætiology.—During the febrile attacks the parasite, *T. cruzi*, can ound only sparingly in the blood, though in the acute disease, as seen in children, it is more abundant. In chronic cases, in which the clinical symptoms may be puzzling, parasites are apparently absent. Apparently in human beings this is a disease of childhood, but in Panama a case has been found by Ludeberg in a man of seventy-seven.

This trypanosome was at first referred to a separate genus, *Schizotrypanum*, on account of its distinctive method of multiplication in the human body. Instead of the longitudinal division which occurs in other species of trypanosomes, this parasite proliferates in the cells of the internal organs, especially in the interior of striated muscles, such as the heart. Two forms, one slender, the other broad, are found in the peripheral blood. In the internal organs multiplication takes place by schizogony (Fig. 20) at a very rapid rate, the resulting forms resembling leishmania bodies which, four days later, become transformed once more into trypanosomes that invade the blood-stream. (For a complete account of the parasite, *see* Appendix, p. 857.) This trypanosome, as it occurs in the blood, can be distinguished from other human trypanosomes by its peculiar " C "-shape, and by the oval shape of the kineto-nucleus. Dividing forms are never seen in the blood. It is by no means certain whether it is related to, or identical with, *Trypanosoma vespertilionis* in bats.

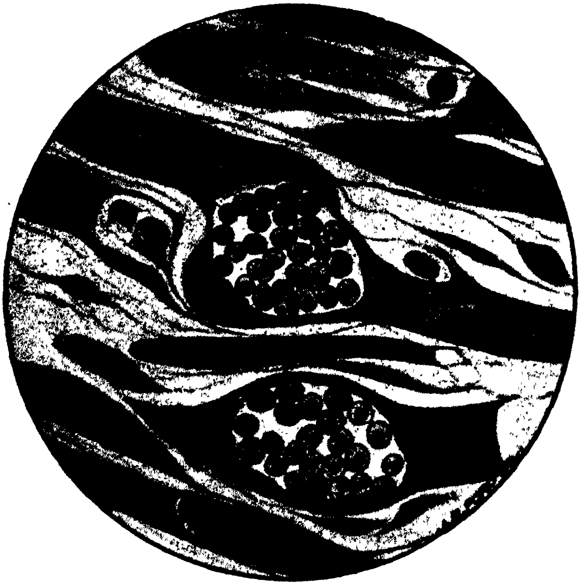


Fig. 20.—*Trypanosoma cruzi* : **schizogony in heart-muscle.**
(*From a preparation by J. Gordon Thomas.*)

T. cruzi is easily cultured on N.N.N. medium, in which it assumes the stunted forms usually seen when it is found in its definitive hosts.

The reservoir-hosts of *T. cruzi* are animals peculiar to the country in which the disease occurs ; there are various species of armadillo, opossum and others (*see* Appendix, p. 859).

Transmission.—The adult trypanosomes are ingested by the intermediary invertebrate host, the bug, *Panstrongylus megistus*,[1] either in its larval, nymphal, or adult stage (Fig. 392, p. 993). After they have passed through many stages in the intestinal canal, in a period of 8–10 days, fully formed trypanosomes, known as "metacyclic" forms, re-appear in the hindgut and are passed out through the fæces of the insect. Infection of man, therefore, probably takes place when the insect defæcates into the wound caused by its bite. The original idea of C. Chagas (1909) that infection is conveyed by the bite of the Panstrongylus has not been confirmed. Mayer stated that infection may be conveyed through the bug in a hereditary manner. In the Northern Argentine the common host appears to be the "Unchuca" (*Triatoma infestans*); in Uruguay *T. rubrivaria*, but many other species of the genera *Panstrongylus*, *Rhodnius*, *Eratyrus* and *Triatoma* can transmit the infection (*see* Appendix, p. 859).

Under experimental conditions, all laboratory animals can be readily infected, and under natural conditions the domestic cat has been found to harbour this trypanosome. Developmental forms have been found in bugs as far north as Utah (*see* p. 143). In infected animals transmission from the parent to the offspring *in utero* can apparently take place, according to C. Chagas, who originally affirmed that congenital transmission frequently takes place in man.

Pathology.—The post-mortem appearances have been described in children. The heart is usually enlarged and there is an excess of yellow or greenish pericardial fluid, sometimes containing a few fibrinous flakes. In microscopic sections there is evidence of diffuse myocarditis and between the muscle fibres there is extensive infiltration of lymphocytes, plasmocytes, macrophages and round cells. There is enlargement of the spleen, parenchymatous degeneration of the liver, and general enlargement of the mesenteric glands. The thyroid gland, as a general rule, is congested and hypertrophied (but *see* p. 147). There is general infiltration of the subcutaneous tissues and thickening of the serous membranes. Subserous ecchymoses are common, and small hæmorrhages in the brain and spinal cord have been described. The skeletal muscles appear to be the seat of election for multiplication of the parasite, and the changes are essentially similar to those in the heart. The gross lesions in the various organs are due to the presence of the parasite. Under the microscope, cyst-like cells, containing leishmania forms, can be found, particularly in the striated muscular fibres, and in those of the heart. When the suprarenal glands are affected, pigmentation of the skin and other evidence of Addison's disease have been observed. The blood does not show great changes, as a rule, but in the acute stages considerable leucocytosis with mononuclear increase has been recorded. The trypanosome may persist without causing severe anæmia for a very long period, and has been found in the blood of a man twenty-five years of age who exhibited no marked symptoms of disease.

Symptoms.—Attention has been drawn to a primary lesion—termed by South American observers a *chagoma*—which results from invasion of the skin and surrounding tissues by proliferating trypanosomes. This takes the form of a local inflammatory swelling, in which leishmanial forms of the parasite multiply within the fat cells. This is followed by a centripetal lymphangitis with formation of nodules along the path of the vessels.

---

[1] This bug has been given various synonyms at various times, and is described in the literature as *Triatoma megista*, *Lamus megistus*, and *Conorhinus megistus*.

Mazza and Freire described similar lesions which they considered hæmatogenous: cutaneous swellings, the size of olives, adherent to the skin, in the suprahyoid, pectoral, and other regions. On the chest they may be as long as 8 cm., raised above the level of the skin, of cartilaginous consistency and violet-red. Some fourteen days after the infecting bite a rash may be seen (Mazza and Mizara) on chest and abdomen, consisting of sharply defined red spots, the size of a pin's head. There is no pain or itching, and the exanthem fades entirely within seven to ten days. Some three weeks from the time of infection œdema of the eyelids, sometimes also of the malar and temporal regions, together with unilateral conjunctivitis (Romaña's sign) is noted (Fig. 21). There are some reasons for believing that occasionally the conjunctiva may be the port of entry for *T. cruzi*, as E. Chagas has shown experimentally (by placing the excreta of bugs on the rabbit conjunctiva). Furthermore, in an accidental laboratory infection recorded by Herr and Brumpt, the site of entry was undoubtedly the conjunctiva, and infection was followed by dacrocystitis, swelling of the face, pyrexia and adenitis. According to Talice and Rial, dacrocystitis may be uni- or bilateral, and is invariably accompanied by facial œdema.

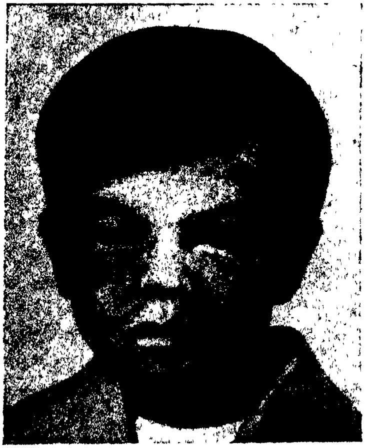


Fig. 21.—Unilateral conjunctivitis as an early sign of infection with *T. cruzi* (*Publication No. 24, Universidad Buenos Aires*).

Enlarged lymphatic glands containing leishmania forms of *T. cruzi* are described by Mazza, in association with the inoculation chagoma, in satellite lymphatic dissemination, as well as generalized lymphadenitis.

The further course of the disease is at present rather obscure. Chagas (1934), in an experimental inoculation of a patient suffering from incurable malignant disease, observed no outstanding manifestations beyond intermittent pyrexia. Trypanosomes appeared in the blood on the thirty-eighth day.

There have been so many discrepancies in the published accounts of the clinical manifestations that it is difficult to describe any particular symptoms as distinctive. Some believe that there are none. Miller, for instance, found his Panama cases distinctly negative, and the trypanosomes vanished from the peripheral blood within the course of a few weeks. Reichenow (1934), working in Guatemala, observed several symptomless cases and thought that the infection may differ in intensity in different countries. There, about 3 per cent. of children of five months of age are infected, and trypanosomes were present in the bloodstream for ten to thirty days.

Chagas and his colleagues described an *acute form* with pyrexia, especially in infants, with general anasarca and thyroid enlargement, and sometimes also with general lymphadenitis. The liver and spleen may both be enlarged. In the terminal stages the child develops symptoms of meningo-encephalitis. Mazza and his colleagues describe an intermittent quotidian type of fever with a double peak as strong presumptive evidence of Chagas's disease. Intermittent fever persists as long as the trypanosome is present in the blood. The *chronic form*, according to Brumpt, may assume a myxœdematous, cardiac or nervous complexion. The former is frequent in children up to fifteen years of age and is characterized by thyroid insufficiency, scanty urine and dry skin. The cardiac type is characterized by cardiac arrhythmia and extrasystoles with brachycardia ; the nervous type by intention tremor and various paralyses.

Kraus has pointed out that it is difficult to distinguish endemic goitre and cretinism, which are frequent in the geographical range of this disease, from acute and chronic trypanosomiasis as depicted by Chagas. Munk has found that in Brazil, where Chagas made his observations, 75 per cent. of the population normally has goitre and there is a cretin in almost every family. It is therefore more than likely that the signs of thyroid insufficiently formally ascribed to Chagas's disease are not, in fact, due to it.

A more recent account by Talice and Rial (1941) described an investigation of 165 acute infections in children in Uruguay. The diagnosis was established by the xeno-diagnostic method. There were two deaths from myocarditis, established at autopsy. More extended practice with the *viscerotome* (p. 342) has established the fact that death in Chagas's disease is usually due to involvement of the myocardium. Meningo-encephalitis has been described as an early or later manifestation.

Diagnosis.—The trypanosome is usually present in very small numbers in the blood-stream, and prolonged search may be required. It may be necessary to collect the blood in citrated saline and subject it to lengthy centrifuging. The parasites may sometimes be found in the cerebrospinal fluid by lumbar puncture, but puncture of the lymphatic glands seldom reveals them. A readier method of diagnosis is to inoculate a guinea-pig with the patient's blood ; the developmental stages of the parasite may be found subsequently in the organs. In the acute form positive results are said to be obtained in 26 per cent. of cases, but in chronic cases animal inoculation is negative. These difficulties in diagnosis have led to the elaboration of a complement-fixation test (Machado, Villela and Bicalho). The antigen is prepared from a glycerin extract of heart and spleen of infected animals. Lacoste, using a glycerin spleen extract of infected puppy, recorded positive reactions in 68·5 per cent. (Machado). Recently, however, artificial cultures of *T. cruzi* have provided a more reliable antigen. The specificity of the test against other forms of human trypanosomiasis must be accepted with reserve, but it seems evident that there is no parallelism between the Machado and the Wassermann reactions. An intradermal test was introduced by Mayer and Pifano, using an extract, " Cruzin," prepared from cultures of *T. cruzi*.

Brumpt suggested a method of xeno-diagnosis which consists in feeding laboratory-bred panstrongylus with the blood of the suspected person, and demonstrating the cyclical development of the trypanosome in the intestinal tract.

Differential diagnosis.—On clinical grounds, Chagas's disease is to be distinguished from endemic goitre, ancylostomiasis, Graves's disease, cretinism, myxœdema, Addison's disease, and other disturbances of the endocrine glands.

Treatment.—Antrypol and most arsenical and antimony compounds are ineffective. Spontaneous recovery in febrile cases has been recorded.

During the last five years treatment has been carried out in Brazil by Mazza and his colleagues with Bayer 7602 (Ac) and since 1940 with Bayer 9736 (As). The former is a quinoline derivative; the latter contains 22 per cent. of arsenic and 5 per cent. of sulphur. The dose of 7602 is 22·2 mgm. per kilo: 5 c.c. of a 3 per cent. solution is given intramuscularly, rising gradually to 20 c.c. According to Talice and Rial, this compound acts directly on the trypanosomes and indirectly reduces the leishmanial forms in the tissues. Five injections are given on alternate days. 9736 is less toxic and better tolerated than 7602, and is given intravenously in 10 per cent. solution. The usual dose is 1·5 c.c. (0·15 grm.) for adult men, and less for children and women, increasing to 3·0 c.c. and even 4·5 c.c. It is given twice or thrice weekly to a maximum total of 50 c.c. (5 grm.) in men, 40 c.c. for women, and 30 c.c. for children.

This new preparation is said to be active against other trypanosomes—*T. gambiense* and *T. rhodesiense*.

Prophylaxis.—This should be directed principally to the suppression of the insect concerned—*Panstrongylus* (*Triatoma*) *megistus* (Fig. 392, p. 993.) This is a large black insect belonging to the family Reduviidæ, well known to the natives, who call it " barbeiro," because, presumably, of its fondness for the face.[1] The nymphs bite and can convey the infection, but the adults, having wings, are more dangerous. In the daytime they live in the grass walls and roofs of the dirty native houses, or of pigsties, coming out after dark in search of their food—blood. Their habits indicate better and cleaner housing, sleeping off the ground, and protection by mosquito-netting. Some fourteen other species of bug have been found infected. Some are of little practical importance.

The fact that the armadillo is the reservoir-host suggests that human habitations should be placed as far away from the burrows of these animals as possible, and that the floors of the houses should be constructed so that the armadillo cannot burrow underneath them. Brumpt has called attention to the fact that one form of reduviid, *Panstrongylus geniculatus*, which normally feeds on the armadillo, is commonly met with in the burrows of a Rock, or *Moco*, cavy, *Kerodon rupestris*, and that the trypanosome can be found in these bugs at great distances from any human habitation. Spontaneous infection of local armadilloes has been reported. It is, therefore, possible that the disease exists independently of man. Robertson has also found large numbers of this trypanosome in the blood of an opossum (*Didelphis*) in Honduras. (*See also* p. 859.)

---

[1] To Americans these insects are known as " kissing-bugs " because of the lesions they produce on the eyes and lips.

CHAPTER V

LEISHMANIASIS

UNDER the title " Leishmaniasis " at least three diseases are included—Kala-azar, Oriental Sore, and Espundia. (Map III.) These, though clinically quite distinct and having each a definite topical and geographical distribution, are all associated with what, optically, at any rate, appears to be the same organism, *Leishmania.*

I. KALA-AZAR (VISCERAL LEISHMANIASIS)

Synonyms. Tropical Splenomegaly ; Black Sickness ; Sirkari Disease ; Sahib's Disease ; Burdwan Fever ; Dum-dum Fever ; Ponos (Greece) ; Mard el Bicha (Malta).

Definition.—An infective disease characterized by chronicity, irregular fever, enlargement of the spleen and often of the liver, and the presence in these and other organs of *Leishmania donovani.*

History.—The earliest description of this disease is by Clarke (1882), who stated that as far back as 1869 the attention of administrative officers in Assam had been directed to a peculiar disease called by the natives kala-azar, the ravages of which decimated, and in some instances almost depopulated, numerous districts in the Garo Hills.

Owing to the absence of malaria parasites, tertian or quartan periodicity, and the inefficacy of quinine in the cases of tropical splenomegaly which Manson had studied in England, he came to regard this disease as non-malarial and as one *sui generis*, and suggested in 1903 that it might be a trypanosome disease. In that year Leishman discovered certain small oval bodies in the spleen-pulp of a soldier who had died of " dum-dum " fever at Netley, and surmised that these bodies represented degenerative forms of a trypanosome. Later, Donovan in London corroborated Leishman's discovery. In December, 1903, Manson and Low found similar bodies in the spleen of a patient from India suffering from the same disease, and were able to show that these bodies were not endocorpuscular parasites. During recent years kala-azar has been discovered in Brazil.

Geographical distribution.—Kala-azar is widely distributed. It occurs in India, especially in Assam, Madras, and along the Ganges and Brahmaputra ; in China, north of the Yangtse in a district between the coast and a line joining Peking, Hankow and, recently, as far south as Canton ; in S. Manchuria ; in the Sudan (Kassala and Blue Nile districts), Western Abyssinia, Northern Kenya, Dakar (Senegal), Chad and French Niger Territory, Darfur, Northern Nigeria, French Guinea, Cameroons and Congo ; Tunis, Tripoli, Morocco, Algeria, and (rarely) Egypt ; in Sicily (Catania), Italy, Corsica, Crete (Canea), Spain (in Madrid and the east and south coasts), Palestine (Shapiro and Btesh), Turkey (Arar and Celik), Bulgaria (Mollow), Hungary (Geldrich), Yugoslavia (Abramov), Cherbourg (de Mouillac), Southern France (Marseilles), Portugal, Greece and the Grecian Archipelago (where the disease known as " ponos " has proved to be infantile kala-azar), Malta, Transjordania, and in Russia west and east of the Caspian, in Transcaucasia and Turkestan. It is found over a wide area in South America.

In South America kala-azar has been found fairly widespread since its discovery by Migone (1913) in Paraguay. Cases were next reported by Romaña from the Chaco in North Argentine. The routine use of the *viscerotome* has brought many other fatal cases to light. Out of 47,000 examinations in North East Brazil, leishmania have been found in 41 ; others have been discovered by E. Chagas in Araca-jú in the state of Sergipe, and by Gatti in Northern Bolivia. Although this parasite was at first provisionally separated as *L. chagasi*, Adler has shown that there is no valid distinction from *L. donovani* and that the South American form readily infects hamsters. In its epidemiology it resembles the Mediterranean form, whilst naturally-infected dogs and cats have been discovered in the endemic areas in Brazil. A few cases have now been discovered in the States of Guárico and Bolivar, Venezuela (Pons, Martinez, Potenza, 1941–2).

Epidemiology.—The main information on epidemiology has been gained from the Assam epidemics which, beginning about 1870, have recurred at irregular intervals since. The main epidemic advanced slowly along the Brahmaputra Valley at the rate of some hundred miles in seven years. Its introduction into a village has usually been traced to some individual from an infected locality. Generally it clung to a place for six years and then disappeared without any apparent change in local conditions. A house seemed to retain the infection for many months, and natives considered it dangerous to re-occupy under a year. In 1922–3 it extended up to the headwaters of the river at Dibrugarh were it had never been known before.

At the present time kala-azar is confined to Assam, Bengal, Bihar and Orissa and the United Provinces as far as Lucknow. It stretches patchily down the East Coast of India as far as Tuticorin.

On account of its deadliness, kala-azar, as it swept onwards, became a terror to the natives. Those suffering from the disease were turned out of the villages ; sometimes they were made unconscious with drink, taken into the jungle and burnt to death. Some villages cut off all communication with neighbouring villages for fear of infection ; other villagers deserted their homes and even migrated to a different district.

The neotropical form occurs in various types of country—in miserable hovels, in dense forests, in desert country and on river banks.

It has been remarked by Kirk that the patchy distribution of kala-azar in the Sudan somewhat resembles that of Brazil. Here the disease is endemic in the Kassala and Fung districts bordering the Abyssinian and Eritrean frontiers. Hence the endemic area extends westwards as far as the White Nile. In the southern Sudan an endemic focus was found in the Kapoeta district, which lies between Abyssinia on the east and Kenya and Uganda on the south. A third endemic area exists in Darfur, the most westerly province of the Sudan.

Archibald and Henderson have shown that kala-azar is found in particularly restricted areas in eastern Sudan, especially along the Blue Nile and its tributaries from the Abyssinian border to within 150 miles south of Khartoum ; there the river flows through open, flat plains of thick loam, where the temperature rarely falls below 60° F. ; the disease particularly attacks ill-fed children.

Giraud states that in the Marseilles district the disease has been apparent since 1922, 146 cases having been recorded. The endemic zone does not extend west of the Rhône in dry, scrubby districts where "*fièvre boutonneuse*" is most abundant.

The outstanding epidemological features of the disease in India and China are that it is confined to rural districts, especially alluvial plains, and does not usually occur above 2,000 feet. The temperature conditions are a monthly mean maximum below 100° F. and a monthly mean minimum above 45° F. In India a high degree of humidity is a common factor : not so in China. In the Mediterranean

the greatest number of cases occur from March to May ; in Assam, in the cooler months from November to February ; in the Sudan, after the rains between August and December ; in China no seasonal incidence has been observed.

Mediterranean form.—In 1904, leishmaniasis was discovered in Tunis by Cathoire, and important studies by the Sergents, Nicolle, and many others showed that the parasite occurs in many of the islands and countries in the Mediterranean basin ; that there it is usually confined to young children—infantile kala-azar—the parasite of which may be a distinct species ; and, further, that, whilst in India dogs are seldom affected, in the Mediterranean basin and in Spain very many of these animals are naturally the subjects of leishmaniasis (*L. caninum*), and in most cases are closely associated with the infantile human disease.

Adler and Theodor have stressed differences between Mediterranean and Indian kala-azar : in the Mediterranean, children under one year are attacked, while in India kala-azar in infants is uncommon. (It must not, however, be thought that Mediterranean adults are always immune.) In the Mediterranean area it is a seasonal disease both in infants and in dogs. On the outskirts of towns and villages it usually appears in April but is very rare after November. In China, too, it has been observed that children are infected solely in the sandfly season. Thus, if a child be born in October the first signs may be observed in the following August.

Nicolle differentiated the parasite, which is morphologically indistinguishable from *L. donovani*, as *Leishmania infantum*, but Brumpt considered that this type is normally a parasite of the dog. The resistance of *L. infantum* to antimony therapy was remarked upon by Adler.

This close association between the canine and human disease is not invariable ; dogs are commonly found infected in Morocco, where human kala-azar is very rare ; in Teheran (Persia) the canine disease is very common : the human disease unknown.

Probably, however, the canine form is more widespread than formerly supposed ; in China, for instance, it has been found in Peking as well as in Manchuria (*see also* Appendix, p. 862).

Infected dogs can be recognized by their extreme emaciation, and thickened and ulcerated skin.

Kala-azar may suddenly break out where previously unsuspected. Thus, Schretzenmayr described a sudden outbreak at the beginning of 1938 amongst Chinese troops in Canton, where the disease had not been previously noted. The first case was diagnosed through the discovery of leishmania in a malaria patient, and during the next five months a further 83 cases were identified. The disease appeared to follow the usual course, but in a number of cases jaundice was a feature. Sudden outbreaks have also been recorded in Nigerian troops in Northern Kenya and Southern Abyssinia during the present war.

Ætiology.—The kala-azar parasite (Plate IV) is included by most authorities in the genus *Leishmania* (though it is morphologically indistinguishable from the genus *Leptomonas*). Two stages are recognized, intracorporeal and extracorporeal. The parasites grow and multiply within the host cells in the spleen, bone marrow and lymph glands. They are transported along protoplasmic processes which pass from cell to cell. They may also be liberated from disrupted cells and taken up by others.

Parasites are also taken up by leucocytes and enter the bloodstream, where most of them are destroyed, although they may survive in numbers sufficient to be detected by blood culture.

Leishman-Donovan bodies are typically parasites of the reticulo-endothelial cells. The parasite is a small ovoid or roundish organism measuring 2–4 μ in diameter. When stained according to Leishman's method it shows two lilac-coloured chromatin masses, one larger than the other, enclosed in a cytoplasm having a faint bluish tint about the periphery. The larger is the trophonucleus ; the small rod-like body is the rhizoplast. It divides by longitudinal fission.

In smear preparations the parasites are often free or in clusters of various numbers, sometimes arranged with great regularity like the merozoites in the segmenting quartan or tertian malaria parasites. Sometimes as many as 50 to 200, or even more, are found together embedded in a structureless matrix or stroma, the remains of the original host-cell.

The parasite can be cultivated outside the body. The medium used by Rogers was citrated blood. When kept at blood-heat the parasites degenerate and disappear, but at a temperature of 20–22° C. they multiply rapidly and assume an elongated motile flagellated form. The flagellum arises from the rhizoplast and projects at the anterior end of the body as in *Leptomonas*, but there is no undulating membrane as in trypanosomes. These flagellated forms measure 12–20 μ in length, and multiply by longitudinal fission. They move actively, flagellum foremost, and tend to agglomerate into rosette groups with their flagella directed centrally. The N.N.N. medium (p. 1017) is now considered the best for culture, but technique must be particular, as bacteriological contamination rapidly kills the parasites. Reichenow's medium of citrated blood and Ringer's solution is also very suitable. A special medium consists of embryonic hamster tissue, heparinized blood, embryonic fluid and spleen extract. Wenyon has succeeded in keeping the parasite alive in successive cultures for fifteen years. The flagellated forms have not been found in the human body, but Wenyon has noted that they may be associated with typical leishman bodies in canine leishmaniasis. The parasite can be communicated to dogs, cats, jackals, monkeys, rats, voles, hamsters and mice, provided that large doses are injected into the peritoneal cavity or into the liver. To infect a dog, it is necessary to inject 2-4 c.c. of a thick emulsion of infected spleen, liver, or bone-marrow. Intravenous injection is by no means so successful, while injections of cultures rarely succeed.

It has now been shown that for growth *Leishmania donovani* and *L. tropica* require ascorbic acid, hæmatin and also an unknown substance in the serum.

Transmission of the parasite.—Adler (1940) has made some interesting and suggestive observations during attempts to reproduce the disease in five patients with advanced malignant disease by injecting flagellates from cultures and from the organs of infected hamsters. The incubation period was five months, before it was possible to demonstrate the parasites in blood or glands. None of the patients developed marked splenomegaly, fever, or other signs of the disease during nine months. The explanation of this anomaly is not at present forthcoming.

The dog is considered the chief reservoir of infection, but in China, a small rodent, the striped hamster (*Cricetulus griseus*), has proved in the laboratory to be extraordinarily susceptible to infection, and this animal has once been found naturally infected in the wild state. In Morocco a small squirrel (*Xerus getulus*) has also once been found similarly infected.

On account of the peculiar topographical distribution of kala-azar in India, Sinton first suggested in 1922[1] that a sandfly (*Phlebotomus*) was the insect vector, and in the same year Napier found a close correspondence between the distribution of *P. argentipes* and the number of kala-azar cases, and noted that this species of sandfly feeds solely on man. A similar suggestion about the leishmania of oriental sore had already been put forward by Wenyon in 1911 and subsequently proved correct by the Sergents in Algiers. Since then a large amount of work on the subject has been performed by Christophers, Shortt, Knowles, Napier, Barraud, Lloyd, and Smith, with the result that a very rapid, intensive development of herpetomonas forms was found to occur in one species of sandfly—*Phlebotomus argentipes*—when fed on the blood of patients suffering from kala-azar. The whole midgut becomes infected and in some individual insects the infection spreads to the pharynx, and even to the buccal cavity (Fig. 22). Subsequently it was found possible to transmit the infection to hamsters by artificially infected sandflies in the laboratory and later (1942) Swaminath, Shortt, and Anderson announced the successful transmission of kala-azar by the bites of sandflies to seven human volunteers. This success, after years of fruitless effort, was obtained by sustaining the sandflies during the two weeks of development of the parasite on fruit-juices (for further details, see p. 951).

In other endemic centres different species of sandfly are involved: *Phlebotomus major* in Eastern Mediterranean; *P. perniciosus* in Western Mediterrean and North Africa; *P. chinensis* and *P. sergenti, var. mongolicus* in China; *P. langeroni* in Sudan; and *P. intermedius* in South America.

An account of the bionomics of the sandfly will be found on p. 951.

Hu and Cash made the most interesting observation that the leishman bodies are taken up by the cells of the reticulo-endothelial system, or clasmatocytes, and these, in experimentally-infected hamsters, become massed as a thick layer of heavily infected tissue lying immediately underneath the skin, though externally no change can be seen. This observation has been confirmed by Hindle. In skin sections from fatal cases of kala-azar a similar condition has been found. All levels of the skin below the epidermis contained leishmania-filled cells collected in large masses about the sweat-glands and arterioles and scattered diffusely throughout the corium. The relationship between this condition and the curious skin eruptions (p. 159) described in India is of interest, and suggests how the parasites may be abstracted by sandflies.

It had been suggested that the transmission may be direct from man to man through the fæces. The evidence for this is based upon the fact that leishmania parasites occur in polypoid masses in some intestinal cases of kala-azar within the intestinal mucosa. Shortt and his colleagues demonstrated Leishman-Donovan bodies in numbers in blood-and-mucus stools in a boy suffering from kala-azar with dysenteric symptoms.

Forkner and Zia in China, on the other hand, discovered leishmania in material obtained by passing a swab over the nasal mucosa of nine kala-azar patients, and parasites were also seen in the material blown from the nose (droplet infection). The tonsils were heavily infected. Material from these situations produced kala-azar in hamsters by intraperitoneal inoculation.

Shortt and Swaminath also reported *Leishmania donovani* in the nasal mucus from cases of Indian kala-azar. In a certain proportion of advanced cases viable parasites are also excreted in the urine.

---

[1] Private communication to Knowles.

That kala-azar may occasionally be a *congenital infection* has been suggested by Carmichael Low and Cooke (1926), who demonstrated the disease in a child seven months old, born in England of a mother who suffered severely from kala-azar during pregnancy. The fact that leishmania is a tissue parasite makes it easier to understand congenital kala-azar than congenital malaria.

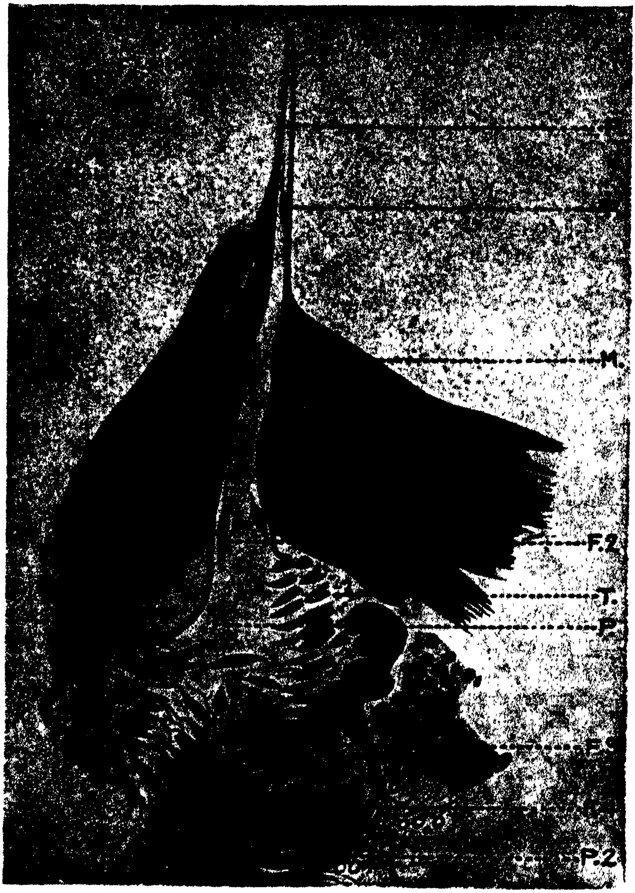


Fig. 22.—Section of *Phlebotomus argentipes*, showing pharyngeal infection with *Leishmania donovani*. (*From Indian Jl. Med. Res.*)

P, lumen of pharynx; P2, posterior termination of pharynx; T, ridges of crinkly portion of pharynx; M, muscles of pharynx; F, flagellate near anterior extremity of pharynx; F2, flagellates anterior to crinkly portion; F3, flagellates breaking free from main mass of growth; F4, massive growth of flagellates at posterior end of pharynx.

Predisposing causes.—Kala-azar attacks both sexes and all ages, but shows a predilection for recently arrived immigrants. In the Mediterranean basin it occurs almost, though not quite, exclusively in children (five months and upwards): in India it occurs at any age.

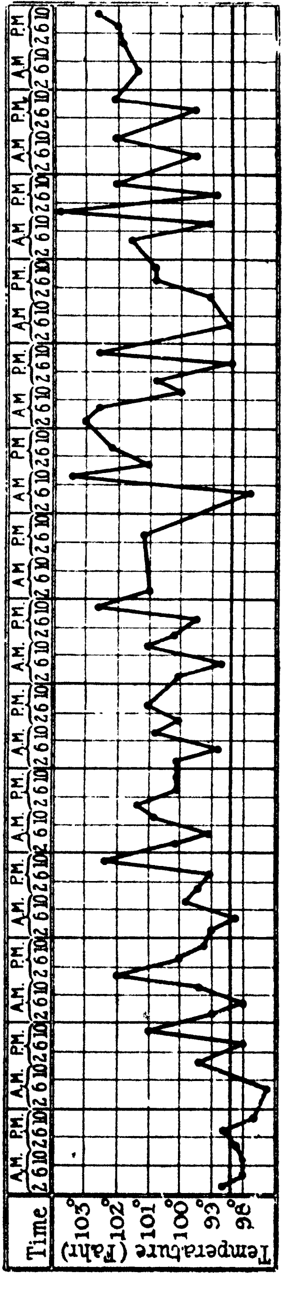


Chart 6.—Four-hourly chart of kala-azar, illustrating the "double rise" in the twenty-four hours.

Pathology.—*The spleen* is grossly enlarged. In the acute stage the capsule is smooth, thickened and nodular, becoming in the chronic form almost cartilaginous. The splenic pulp is increased in amount and very friable. There are usually numerous infarctions. The hypertrophy is due to congestion and reticulo-endothelial proliferation; it is estimated that one-fifth of the spleen substance is composed of parasites. There is little fibrosis. The leishmania are numerically more abundant in the spleen than in any other organ.

The liver is also enlarged, brown or mottled, almost nutmeg in appearance. The Kupffer cells are packed with parasites. There is some pressure atrophy of the parenchyma cells and, finally, in the chronic stage, a fine intralobular cirrhosis.

The bone-marrow is reddish, containing abundant parasites; the destruction may be so extensive that very little blood-forming tissue remains.

The kidneys contain few parasites, which are carried there by the bloodstream. The scanty parasites which have been found in the urine are probably derived from invasion of the bladder.

The lungs show no parasites, but are liable to secondary bacterial invasion on account of the leucopenia which is such a constant feature of this disease.

In the *gastro-intestinal tract* there is proliferation of reticulo-endothelial cells, especially in the duodenum and jejunum. The villi may become grossly hypertrophied and swollen by packed parasitized cells. Small ulcerations are not uncommon and parasites can be demonstrated in them.

The lymphatic glands are generally enlarged and congested, especially the mesenteric group, and the tissue is usually invaded by large numbers of leishmania. There is also hypertrophy of the retropharyngeal lymphoid tissue, and leishman bodies can be found in nasal and pharyngeal secretions.

The underlying essential pathology of this disease is blockage of the endothelial system (Hu and Cash). The parasites are engulfed by the endothelial cells; they then multiply until the cell ruptures and the organisms, escaping into the blood-stream, are transported to other organs.

Symptoms.—The *incubation period* is difficult to fix. In one Englishman under Manson's care the time that elapsed from his arrival in perfect health in the endemic region and the onset of fever which terminated in kala-azar (diagnosed microscopically both before and after death) was under ten days. Kirk, on the other hand, from accurate observations in the Sudan, fixes the period between three and six months. In some artificially-infected dogs, the disease, like dermal leishmaniasis, may remain latent for months.

A primary lesion in the form of one or more minute dark red papules on the face was described by Mirzoian in Central Asia.

The onset may be gradual or sudden; if gradual, it cannot be diagnosed at all on clinical grounds. If sudden, there is usually high fever, which may be preceded by rigor and, in some cases, by vomiting. The initial fever may be very severe (Charts 6, 7). It is intermittent in some instances, more frequently remittent, often with a double remission in the twenty-four hours, resembling that of subtertian malaria. It lasts from two to six weeks, occasionally longer. Waves of fever, separated by apyrexial

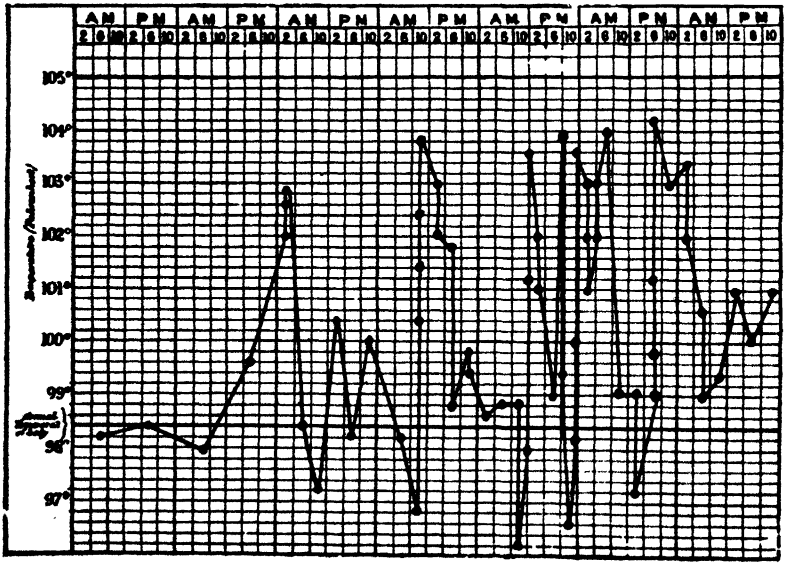


Chart 7.—Temperature chart of acute kala-azar, showing "double crisis."
(Dr. G. Carmichael Low.)

periods, may often simulate undulant fever, and during the pyrexial periods both the liver and the spleen enlarge. There may be daily rigors, so that malaria may be suspected. A four-hourly temperature chart in a well-marked case may show a double or even a triple rise of fever.

The spleen is usually enlarged from the commencement of the illness, whilst the liver does not become appreciably bigger until the disease has lasted some months. In rare cases in the initial stages, enlargement of the spleen may not be an outstanding feature, and the Editor has seen cases in which hepatomegaly persisted for some months before the spleen became palpable. Generalized lymphadenitis is common, and in China and in Brazil, uniform enlargement of the cervical glands has been observed. In India, too, cervical adenitis may sometimes occur, and sometimes, too, there is enlargement of the epitrochlear glands.

Then comes a period of apyrexia and general improvement, to be followed once more by fever, splenic and hepatic enlargement, and perhaps tenderness. In women amenorrhœa is often an early symptom. In this way spells of fever and apyrexia recur for months, absolutely unchecked by quinine, until finally a low form of fever, rarely over 102°F. becomes more or less persistent. Profuse sweats are common during remissions at all stages of the fever; in the more chronic stage rigors occur exceptionally. Pains in the limbs often suggest rheumatism. When the disease is thoroughly established, emaciation and anæmia become noticeable, and, together with the enlargement of the liver and spleen, produce a typical appearance. Œdema of the legs, sometimes circumscribed, may be present. In many cases the skin acquires a strange earthy-grey colour; this dusky pigmentation, which has given rise to the native name, kala-azar, " the black disease," is best seen on the feet, hands and abdomen in Europeans, though very difficult to distinguish in dark-skinned natives. The hair is apt to become dull, dry, and brittle, and may fall out; petechiæ, in the axillæ especially, are not unusual; epistaxis and bleeding from the gums are common. This condition of chronic fever, enlargement of spleen and liver, emaciation, and anæmia may continue for months or even one or two years, until improvement sets in. More usually—96 per cent. of cases (Rogers), 150 recoveries in 2,000 cases (Price), 24 recoveries in 100 cases (Lignos)—the patient is cut off by some intercurrent disease, especially dysentery.

One outstanding clinical feature is that, in spite of the patient's weak, emaciated condition, the pyrexia, and the protuberant abdomen due to splenic enlargement, he preserves a good appetite and a clean tongue; he may be working with a temperature of 102° F. quite unaware that he has fever (Fig. 23). There is no malaise or apathy. In this respect kala-azar differs from malaria and other toxic fevers, such as typhoid. Kala-azar usually lasts several years, but the Sudan cases, especially, may run an acute course in about five months. In the terminal stages ascites may develop, due to gradual cirrhosis of the liver. Anæmia may become progressively severe. Hæmic murmurs of the heart are often heard. Hæmorrhages may occur from any part of the body, and purpuric patches may appear on the skin after local injury. Death may ensue from several causes. When due to the disease alone it results from exhaustion.

Dysenteric symptoms are frequent, and may be due to intestinal lesions caused by Leishman-Donovan bodies, or to a superadded infection with amœbic or bacillary dysentery. Broncho-pneumonia and noma are frequent terminal symptoms. Proctor, however, reports that noma can be arrested in the early stages by scrupulous daily inspection of the mouth. Should a grey line of ulceration on the gums be seen, it should be energetically treated with carbolic acid and spirit. It may be that this gangrenous process is not so much due to the kala-azar as to the leucopenia, and it has a striking analogy in the angina which is so characteristic of agranulocytosis.

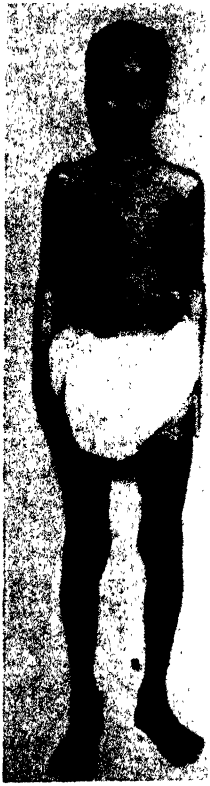


Fig. 23.—Kala-azar in Indian boy. (*Dr. L. E. Napier.*)

Blood changes.—*Anæmia* is invariable in advanced cases and is due to destruction of the erythroblastic tissue of the bone marrow. These changes are not so obvious in the infantile form. The red blood corpuscles are often reduced to 2,500,000 per cu. mm. with a corresponding and parallel fall in hæmoglobin.

The most remarkable change is the *leucopenia*. The leucocytes are reduced below 3,000 per c.mm. in 95 per cent. of cases ; below 2,000 in 73 per cent. ; and 1,000 in 42 per cent. The proportion of leucocytes to erythrocytes, normally 1 to 750, stands at 1 to 1,500 or even 1 to 2,000. The differential count usually shows a relative increase of lymphocytes, a moderate increase of large mononuclears and almost complete absence of eosinophils. (The biochemistry of the blood is described on p. 163. Owing to the increase of euglobulin in the serum, Henry's reaction is usually positive.) The liability of kala-azar patients to pneumonia and superadded septic infections is ascribed to leucopenia.

The reduction in leucocytes may proceed to acute *agranulocytosis* (Forkner and Zia in China, Shortt and Swaminath in India, and Gritti in Italy).

Davies and Wingfield (1941) have studied one such case in detail. The patient, who was undergoing treatment by neostibosan, had a bout of pyrexia with rigors, associated with buccal ulcers and angina. Agranulocytosis lasted for five days. There was no response to pentnucleotide, but recovery took place after blood transfusion and intravenous injections of 15 mm. of adrenalin (1 in 1000), at ten minutes intervals.

Huang studied a series with this complication exhibiting throat and skin lesions. Some cases were due to leishmania infection, whilst others appear to be caused by antimony treatment ; the latter are the most severe. A blood platelet count of over 100,000 per cu. mm. may be regarded as favourable. The blood pressure sinks appreciably, the systolic reading falling below 100 mm. of mercury.

Acute toxic kala-azar.—When kala-azar breaks out in a new area, especially in the stress of war, it may assume an acute and almost unrecognizable form. This happened in Nigerian regiments during the recent Abyssinian campaign, as reported by Cole, Cosgrave and Robinson. The case mortality-rate of one outbreak was almost 50 per cent. The onset was sudden, often with rigors, headache, epistaxis, high fever, abdominal pain, vomiting, painful liver and spleen. In a proportion of cases the course of the disease was so rapid that the spleen never became palpable. Renal symptoms were noted, whilst the urine contained albumin and casts. The complications were hæmorrhagic : bleeding from gums, skin petechiæ, and blood-and-mucus stools. Œdema was noted in three cases, and in three there was general anasarca (Cole, 1944).

Infantile kala-azar.—The symptoms of the infantile form are, on the whole, similar to those of the adult type and differ only to the extent that might be expected in a disease of very young children. The onset is usually insidious, with some fever and gastro-intestinal upset. The spleen and liver enlarge, and the child becomes apathetic, anæmia and emaciated, and the abdomen protrudes. Irregular attacks of fever occur, and the child often suffers from epistaxis, bleeding from the gums, and hæmorrhages into the skin. The lymphatic glands are usually enlarged. The clinical picture resembles infantile splenic anæmia (Banti's disease).

Dermal leishmanoid.—A cutaneous form of leishmaniasis, in which the parasites occur in nodules of the skin on face, forearms, inner aspects of thighs and pubic regions, was first reported by Christophers in India in 1904, and Thomson and Balfour in the Sudan in 1909, and has since been observed in the Blue Nile (Kassala) districts. It was described by Brahmachari in India under the name of "dermal leishmanoid," or "post-kala-azar leishmaniasis." It is certainly a sequel to generalized infection with *L. donovani*, as more than half the patients who exhibit this curious eruption have suffered from kala-azar about one year previously and have been given antimony treatment. The leishmania are found in smears from the nodules, and cultures have been obtained from the lesions. It is not at all clear at present what the significance of this phenomenon is, or what factor causes the organisms to establish themselves in the skin. This condition occurs in all classes of the community, in persons of all ages and both sexes. Though not all give a history of kala-azar, it is generally conceded that leishmanoid is a sequela of generalized leishmania infection, and the dermal lesions usually make their appearance from one to two years after all signs of visceral disease have disappeared.

The first, or depigmented, stage usually appears as colourless patches on the face and upper extremities, gradually spreading to the remainder of the body. Minute dots gradually enlarge to irregular areas half an inch in diameter, which occasionally tend to break down. There is œdema of the subpapillary tissues accompanied by dilatation of the vessels. Below this there is infiltration by macrophages of the subpapillary plexus. The second, or nodular stage, is seen about two years after antimony treatment. (Fig. 24.) Usually the nodules replace the depigmented patches, but there are certain areas, such as the face, where the nodules appear much earlier than in other parts of the body. They may extend to the mucous membranes and ears, and may closely resemble leprosy.

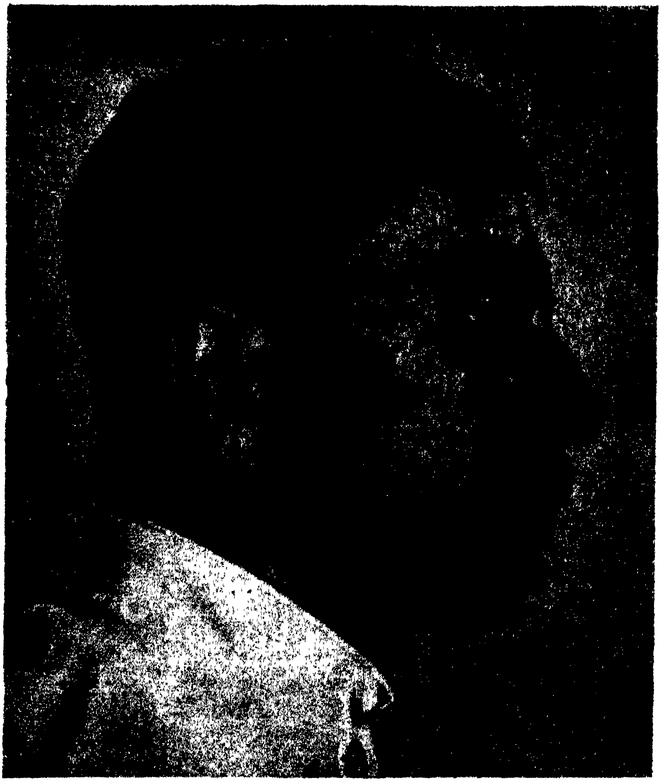


Fig. 24.—Dermal leishmanoid. Extensive nodular lesions on face and ears. (*Acton and Napier, Ind. Jl. Med. Res.*)

In the Sudan a punctate cutaneous eruption has been described by Kirk, and in the larger nodules leishmania can be demonstrated, especially towards the completion of antimony treatment. The epithelium is thin and the subpapillary layer is œdematous, with atrophy of the fibrous and elastic tissue. Subjacent to this œdematous area is a granulomatous mass consisting of proliferating macrophages. There is also a xanthomatous form. These lesions are raised, orange-coloured plaques which are painless and do not ulcerate.

Preliminary treatment with massive doses of potassium iodide causes the nodules to ulcerate and they then become susceptible to intravenous injections of aminostiburea.

Association of kala-azar with oriental sore.—It was formerly considered that these two clinical entities were never associated, but this appears to be by no means invariable. Originally Christopherson, and then Kirk and Macdonald in the Sudan, described cases where visceral, cutaneous, and even mucosal lesions are present in the same individual. In China, too, Wang found subcutaneous nodules, composed of endothelial cells with many leishmania. In the Sudan form of kala-azar, circumscribed cutaneous ulcers with a tendency to coalesce are the most frequent.

Eye lesions.—R. E. Wright showed that when eye lesions occur in kala-azar, as in malaria, they are due to retinal hæmorrhages in the posterior segment of the eye.

Immunity.—There is no definite evidence of the mechanism of immunity to kala-azar. It has been shown that immunization against bacterial infection is not interfered with by the blockage of the reticulo-endothelial system which results from generalized leishmania infection.

Diagnosis.—Irregular chronic fever with enlargement of the spleen and diminution in the number of leucocytes in patients from the endemic zone suggests kala-azar. Examination of the blood can at once exclude leucocythæmia and also malaria, if taken together with absence of tertian or quartan periodicity and the inefficacy of quinine or atebrin.

Splenic puncture must not be lightly undertaken. A preliminary examination of the blood should always be made to ascertain the degree of anæmia, to exclude leucocythæmia and to obviate the necessity for splenic puncture, and the attendant risk of fatal hæmorrhage so easily induced in that disease. *Liver puncture.*—When the liver is enlarged, it should be punctured instead of the spleen as it is less vascular and less easily torn, but, as a general rule, the parasites are not so abundant and the results are therefore unsatisfactory. In performing puncture, the abdomen should be firmly fixed with a binder to prevent, as far as possible, movement of the diaphragm and consequent risk of tearing the punctured organ. The patient should be injected with $\frac{1}{100}$ gr. of atropine one hour previously, and the puncture site infiltrated with novocain to deaden pain. It is wise to give 30 gr. of calcium lactate the evening before and on the morning of the puncture. The lower border of the spleen or liver should be steadied by the hand. A hypodermic needle, scrupulously clean and dry,[1] and connected with the barrel of the syringe by a short length of rubber tubing, should be used, the patient being directed not to start or breathe when the puncture is being made. The type of needle is most important. The bore should be neither too big nor too small. The Editor has found Maw's size No. 10, with a shaft 40 mm. in length, the most suitable, and Napier has devised a special spleen-puncture syringe (Fig. 25). Failure to draw blood is not to be regarded as failure to obtain material

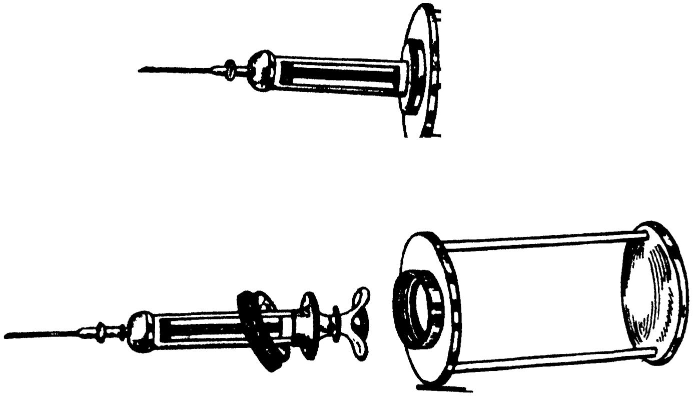


Fig. 25.—Spleen puncturing syringe. (*After Dr. L. E. Napier.*)

---

[1] A trace of water in the needle will distort or burst the parasite and render it unrecognizable.

for microscopical examination ; on the contrary, it is an advantage, as the object is to procure spleen or liver pulp, not blood. After the contents of the needle have been blown out on a slide, it may be trans-illuminated by an electric pocket-torch to discover the minute sago-like masses of splenic tissue. A film should then be spread and, after it has dried, stained by Leishman's or Giemsa's method, and then examined with a $\frac{1}{12}$ in. objective. Adler points out the desirability of culturing the material obtained on suitable media, as the parasites may be so few as to be missed by examination of smears.

Splenic puncture is not advisable in infants on account of the danger of laceration and intraperitoneal hæmorrhage. For puncturing the liver the site of election is the 7th or 8th intercostal space in the mammary line.

Lymphatic gland puncture is efficient and simple (Kirk and Sati), generally most efficacious in the glands of the groin. The lymph is massaged into the needle, into which it runs by capillary attraction. The skin is sterilized, and the glands identified, pulled up from the underlying tissues and steadied by juxtaposition of the index finger and thumb. A *dry* sterile needle (hypodermic 16) is pushed through the skin into the gland, and it is easy to feel when the needle has entered. It is held there for a second or two, then quickly withdrawn and attached to a small syringe, by which the gland " juice " in the needle can be blown on to a slide and stained by Leishman stain.

Sternal puncture was advocated as a diagnostic procedure by Lovando in Athens, Andrew Ura, Regli, L. Brumpt and Benhamou. It is safer and surer than spleen puncture, and Chung in Peking considered it the best method, and that a local anæsthetic is seldom necessary. A shortened lumbar puncture needle is inserted at an angle of 30 or 40 degrees at the level of the second or third interspace. The needle, with contained stylet, is pushed with a boring action through the bony lamina. When the marrow is reached, the stylet is removed and a syringe for aspiration attached. Even in the absence of parasites, a myelogram is said to be distinctive. The average is : granulocytes 23, erythoblasts 24, hyaline leucocytes 53. Normally granulocytes are four times as numerous as erythroblasts and 3·5 times as hyaline leucocytes.

Bone puncture.—Giraud considered tibial puncture the method of election in young children. The point selected is the inner surface of the tibial epiphysis, 1 cm. below the knee joint. A fine trocar and cannula is passed until entry into the spongy tissue is signalized by loss of resistance. The bone marrow changes indicate regenerative action of the normoblastic type and inhibition of myeloid cells (*see* above). The material should be sown on appropriate media in every case, as parasites are usually too few to detect in smears.

Blood examination.—The frequency with which this parasite has been found by blood examination varies in different localities. In some places, as in Madras and Assam, Leishman-Donovan bodies are evident in about 60 per cent. of all cases examined, enclosed within large mononuclear cells, and to a lesser extent within polymorphonuclear leucocytes.

Knowles and Das Gupta used thick films, prepared by placing four drops of blood on a slide, mixed so as to cover an area of $\frac{1}{2}$ sq. in. The film is covered with a Petri dish and dried at 37° C. for two hours. It is then flooded with glacial acetic acid (2·5 per cent.), 4 parts, crystalline tartaric acid (2 per cent.), 1 part, for five minutes. After tilting off the fluid, the film should be fixed with methyl alcohol and covered with dilute

Giemsa stain. It is claimed that by this method leishmania can be found in 67 per cent. of cases.

Shortt and his colleagues place a small drop at one end of a slide with a second one applied in the usual manner, and spread a thin film. At this stage the spreading slide is abruptly lifted, so that the blood-smear ends in a straight edge which is somewhat thicker than the rest of the smear.

Young and Van Sant obtained good results by centrifuging 5 c.c. of blood in Locke's solution (modified) (sodium chloride 9 grm., potassium chloride 0·4 grm., calcium chloride 0·2 grm., sodium citrate 10 grm., distilled water 1,000 c.c.) at a speed of 750 revolutions. The parasites are readily discovered in films from the bottom of the centrifuge-tube.

It is stated that parasites are more readily found in the blood-stream after intravenous injection of 10 min. of 1 in 1,000 solution of adrenalin. Chopra claimed that intravenous injection of pentavalent antimony compounds causes contraction of the spleen and appearance of the parasites in the peripheral blood.

Wenyon stated that the presence of the parasite in the peripheral blood can be more easily verified by blood-culture. For this purpose 2 c.c. of blood is drawn off by means of a 2 c.c. syringe, and mingled with 1 c.c. of 6 per cent. citrate solution in a sterile tube ; this is placed in a cool incubator and allowed to sediment for two hours. The deposit is drawn up by a pipette, inoculated into two or more tubes of N.N.N. medium, and placed in a cool incubator. Examination of cultures is made about the tenth day, when flagellate forms are observed, but observation must be continued for at least twenty days. Splenic pulp may be cultured in the same manner.

Biochemical reactions.—The alkalinity of the blood is said to be decreased, while in some cases the coagulation-time is very considerably prolonged.

A specific *complement fixation* test was introduced by Niyogi and Ray (1942). The antigen is prepared from washed flagellates from 48-hour cultures of *L. donovani :* 60 millions per c.c. was found to be reliable. The suspensions were shaken for 48 hours in a machine and then kept in a refrigerator.

Aldehyde test (or the serum-formalin reaction (Brahmachari[1] and Napier) proved to be very useful as a method of diagnosing kala-azar on a large scale. About 5 c.c. of blood is withdrawn from a vein and allowed to stand a sufficient time for the serum to separate ; 1 c.c. of *clear* serum is then placed in a test-tube (3 by ⅜ in.), and to this 1 drop of 30 per cent. formaldehyde, or commercial formalin, is added. The serum is at once well shaken and placed in a test-tube rack at room-temperature. In a certain proportion of cases of kala-azar, especially in chronic cases, solidification of the serum takes place within a space of three to twenty minutes, but a control of normal serum should always be made. Napier himself states that " jellification " with opacity (like the white of an egg) of the serum may be taken as diagnostic of kala-azar if the disease is of more than three or four months' standing, but milkiness without solidification only takes place in early cases. But in exceptional cases even this reaction does not become apparent until an advanced stage. Should the serum be hæmoglobin-stained, this will change to chocolate-brown after twenty-four hours. In certain cases of syphilis, leprosy, hepatic cirrhosis, bilharziasis, subacute endocarditis, lymphadenoma, phthisis, and malaria the serum will solidify, but remains clear and does not become opalescent as in kala-azar. The reaction, which occurs in twenty minutes, is given as +++; after two hours as ++, and after twenty-four hours as +.

---

[1] As a matter of historical interest this test was first introduced in 1921 by Spackman as a modification of the formol-gel test of Gate and Papacostas.

Other so-called lability reactions are also positive, as for instance, the Takata-Ara which is used for the diagnosis of liver cirrhosis and other diseases with increase of globulin in the blood: 0·02 c.c. of blood is mixed with 0·6 c.c. of distilled water. Haziness or cloudiness develops after five minutes and the globulin test is positive; after fifteen minutes a distinct precipitate occurs. The distilled water must be neutral with *p*H varying between 7 and 7·2.

In kala-azar it has been proved that the plasma globulins are increased, while the albumins are diminished. In kala-azar, the albumins are 2·8; the globulins 4·0, as compared to 4·5 and 2·0 per cent. respectively in the normal. Lloyd and Powell constructed a typical globulin curve of kala-azar in which euglobulin constitutes 40–50 per cent. of the total. Auto-agglutination of the red blood-corpuscles is often noted, as in trypanosomiasis, more especially in advanced cases.

Antimony test.—Chopra pointed out, and Napier confirmed, the curious fact that the addition of a 4 per cent. solution of pentavalent antimony compounds to kala-azar serum causes a heavy precipitate, the amount of which corresponds to the efficacy of that compound in the treatment of the disease.

The method is as follows: One to two drops of blood from the pricked finger are allowed to flow into a Dreyer's tube in which has been placed 0·25 c.c. of a 2 per cent. potassium acetate solution. The tube is then inverted to mix the contents; a little of this mixture is transferred to another tube, and a 4 per cent. solution of the antimony compound (stiburea, for example) is added by means of a capillary pipette and allowed to percolate along the wall, so that it comes to lie below the blood mixture. In a positive case a flocculent precipitate forms at the junction. In very early cases it may not appear for 10–15 minutes: in the more advanced it is immediate. The character of the precipitate is important in kala-azar; it is so flocculent that it is not easily broken up by shaking, and it does not disappear in twenty-four hours.

In cases of doubt it is a good procedure to dilute the serum with 10 volumes of distilled water and to repeat the test. Alcohol must not be used for cleansing the finger. André (1932) claimed that the results are improved by reading the opalescence produced in kala-azar serum by urea stibamine by means of the "Vernes-Bricq-Yvon" photometer.

Napier stated that the aldehyde and antimony tests are almost of equal value. Out of 201 cases of kala-azar diagnosed by discovery of the parasite, 156 gave a positive antimony test, and 128 the aldehyde test.

Sensitization tests.—Intradermal injections of alkalinized extracts of *L. donovani* cultures usually give positive reactions, but their diagnostic value is open to doubt.

Differential diagnosis has to be made from splenic anæmia, malignant endocarditis, cirrhosis of the liver, trypanosomiasis, and Egyptian splenomegaly (*Bilharzia mansoni*) which, save for the absence of the parasite and the characteristic pyrexia, may closely simulate kala-azar. Visceral syphilis, with enlargement of liver and spleen, malignant disease and tuberculosis of the spleen, may have to be excluded. In China and Japan kala-azar may have to be differentiated from intestinal bilharziasis (*Bilharzia japonica*), in which enlargement of the abdominal organs may occur. The remarkably clean tongue and the good appetite serve in some measure to differentiate kala-azar from chronic malaria, to which may be added the considerable emaciation, absence of extreme anæmia, double daily rise of temperature (in 88 per cent. of cases), distension of the superficial abdominal veins, and pigmentation of the extremities.

TREATMENT

Antimony treatment.—At first intravenous antimony tartrate (*sodium-antimony tartrate*) or, less commonly, potassium antimony tartrate, was employed by the method introduced by Vianna in Brazil for dermal leishmaniasis. The results achieved in India by Rogers, Mackie and others were very encouraging, and subsequently led to the development of more highly organized compounds of antimony, such as the pentavalent salts.

Neoantimosan (Fouadin) (*see* p. 686), a trivalent antimony compound, by intravenous or intramuscular injections, has been used for treatment, but is not so satisfactory as the pentavalent compounds.

The reaction of a kala-azar patient to antimony treatment can be assessed in various ways: in improvement in the clinical condition, increase in body-weight, shrinkage in size of the spleen and of the liver, and increase of the leucocyte count. The relative proportion of serum globulin can be gauged by the aldehyde test, which is positive so long as the parasites remain active in the body and, moreover, persists for two to three months after the patient has, to all external appearances, completely recovered.

Even in cases reacting favourably to treatment, it is stated that apparently unchanged and viable parasites may be found in the spleen even after a gramme or more of antimony preparations has been injected, but by the time the spleen has retracted within the costal margin, the Leishman-Donovan bodies have disappeared altogether.

1. Treatment with pentavalent compounds of antimony.—(*a*) *Neostibosan* (formerly known as von Heyden 693) is the amino salt of para-aminophenylstibinic acid, contains 40 per cent. of metallic antimony, and is comparatively non-toxic. It may be given in a strength of 25 per cent., either intravenously or intramuscularly. The doses may be given daily but, generally speaking, alternate days are preferable. The initial dose for an adult is 0·1 grm., the second 0·2 grm., the third 0·3 grm. This compound appears to be especially well tolerated. About ten injections are required for an average case, and a total of 2·7–4·0 grm. is usually necessary to effect a cure.

It has been pointed out by Neumann that in Malta, quite apart from the difficulties in administration, intravenous injections of antimony in children are apt to be followed by broncho-pneumonia, but neostibosan, when given intramuscularly, is almost equal in effect to the intravenous method. A dose of 2·5 grm. suffices within a period of six weeks. Since this method has been employed, noma has not been seen and broncho-pneumonia is less frequent.

(*b*) *Urea stibamine* (stiburea—$C_7H_{12}O_6N_2Sb$), is a compound of urea with stibamine (*p*-aminophenylstibinic acid), and was introduced by Brahmachari. This compound is apt to undergo chemical changes if exposed to the air. Urea stibamine is undoubtedly an efficient preparation and often succeeds where other pentavalent salts fail; in resistant cases it may be given in combination with neostibosan; the Editor has seen successful results from this method. The total amount to effect a cure is about 3 grm. The usual length of treatment is one month; if, for some reason or other, an intermission in treatment takes place, the parasites tend to become antimony-fast. Urea stibamine may be given intramuscularly to infants in doses from 0·01–0·08 grm. in 1–2 c.c. distilled water, a total of 0·65 grm. being necessary.

(*e*) *Solustibosan* 561 (pentavalent antimony gluconate) was introduced by Kikuth and H. Schmidt, who considered it in many ways superior to neostibosan in the treatment of kala-azar. It is issued in ampoules of sterile soluble isotonic neutral solution in water so that 1 c.c. contains 20 mg. of antimony; thus 6 c.c. corresponds to 0·39 grm. of neostibosan and contains 0·126 grm. of antimony.

Struthers and Yates reported upon its application in China (Tsinan). They employed it on the basis that 2 c.c. of solustibosan is approximately equal to 0·1 grm. of neostibosan. The former treated 29 and the latter 9 cases. In some, it is said, the course was completed and a cure effected in nine days. This drug is usually given intravenously, though, being isotonic, it may also be injected by the intramuscular route. In infantile kala-azar solustibosan is best given in oily suspension (1 c.c. representing 0·054 grm. pentavalent antimony), intramuscularly: 2 c.c. for each kilo of body-weight. (For other compounds see pp. 823, 824.)

Toxic effects of antimony treatment.—Christopherson states that "metallic taste in the mouth and throat need scarcely be considered as poisoning, but vomiting, giddiness, delirium, a considerable rise or fall in temperature, diarrhœa, and cramp in calves should be taken seriously. They are danger signals and, when they occur, the injections should be temporarily suspended. Rapid pulse, cold, clammy skin, signs of collapse, in fact, are serious symptoms of poisoning." Discomfort or pain in the chest, colic, headache, severe arthritic pains in shoulder and other joints, and even jaundice may be noted.

Disagreeable symptoms are less likely to ensue since the introduction of the pentavalent salts of antimony. The death-rate among kala-azar patients has undoubtedly been much reduced by their use (42 per cent. in 1925, according to Napier). Jaundice is, perhaps, more common. It is by no means certain how antimony destroys the leishmania parasites; *in vitro*, and also *in vivo*, the action is certainly not a direct one.

2. **Diamidino stilbene** (**stilbamidine**).—The Mediterranean and Sudanese forms of kala-azar having proved more refractory to antimony treatment, and requiring on an average double the amount necessary to cure the Indian strain, Yorke searched for a more efficient drug, and found *diamidino stilbene* (M. & B. 744). During the last three years there have been numerous communications on this drug by Adams and Yorke, Adler, Ternomoretz, Rachmilewitz, Kirk, Sati, Napier, Sen and Wingfield.

The therapeutic dose is assessed at 1 mgm. per kilo. by the intravenous or intramuscular routes. (The range is from 0·1–2 mgm. per kilo). Yorke administered 860 mgm. within eight days, whilst Napier and Sen increased the dose on occasions to 2 mgm. per kilo., and in one case of post kala-azar leishmaniasis gave a total of twenty injections—0·95 grm. Eight to ten injections on successive days are advised.

Napier and his colleagues (1942) published results in a series of 100 Indian patients to whom the drug was given intravenously in 1 per cent. solution. They concluded that the introduction of stilbamidine constitutes a great advance in the treatment of kala-azar. Antimony-resistant cases respond particularly favourably. Weight for weight, only about one-quarter as much stilbamidine is required per case as neostibosan: 60 grm.

suffices to cure 100 patients. The drug is apparently of no value in the treatment of dermal leishmanoid or cutaneous leishmaniasis.

On the whole, it is well tolerated in graduated daily doses of 50–200 mgm. each up to 2·5 grm. Somers (1944) gave Sudanese natives 1–4 mgm. per kg. body weight, the total dose being 3·01–4·88 grm. at intervals of 1–3 days (*see* p. 821). It should be dissolved in 10 c.c. of water and injected very slowly, otherwise it may cause vomiting. Administration is followed by a very considerable fall in blood pressure and also by a temporary decrease in blood sugar. The patient becomes flushed, with a burning sensation in chest and abdomen and slight dyspnœa, probably the result of stimulation of the parasympathetic system; these effects can be mitigated by adrenalin. Trigeminal neuralgia has been recorded as an after-effect. A second course can be given three weeks after the termination of the first, with apparent benefit. In contradistinction to antimony compounds, no improvement takes place in the patient during the actual course of treatment. There is no drop in pyrexia or diminution in size of liver or spleen, but afterwards gradual amelioration is noted, and in a further four weeks, signs and symptoms disappear. Toxic manifestations, in some cases fatal, have been reported, due to liver necrosis, which may be delayed for a month or longer after cessation of treatment. Solutions of stilbamide exposed to light develop a toxic product, 4 : 4′-diamidino-phenyl-benzyl-carbinol. The injections must, therefore, always be freshly prepared.

The discovery of diamidino stilbene is the product of research by Ewins who synthesized a series of aromatic compounds containing the amidine group. The most active aromatic diamidines are 4 : 4′ diamidino stilbene; 4 : 4′ diamidino diophenoxy propane; and 4 : 4′ diamidino diphenoxy pentane. The most satisfactory from the therapeutic viewpoint is the first. It was tried out on *Babesia canis* by Yorke, and subsequently on leishmaniasis in hamsters by Adler.

Prognosis.—Kala-azar is, in the great majority of cases, a chronic disease; but acute cases are noted in the early stages of an epidemic. Marked intestinal disturbance, ascites and liver cirrhosis indicate a bad prognosis, as does also extreme leucopenia. The prognosis is naturally affected by coincident infections such as malaria, the dysenteries and ancylostomiasis. Napier pointed out that with superadded pulmonary tuberculosis it is especially grave; but there is a tendency to spontaneous cure in about 10 per cent. of cases. The oft-repeated statement that, owing to the introduction of the antimony treatment, a 95-per-cent. mortality-rate has been converted to an equally high recovery-rate, is, therefore, not strictly true.

Prophylaxis.—Domestic and personal cleanliness is of great importance. Infected dogs should be destroyed, and in the endemic districts dogs should be kept away from association with man. Papantonakis proved that destruction of dogs in Canea in 1933 was followed by marked decrease of kala-azar in the following year. By segregating the sick, burning houses, clothing and furniture, and providing new huts, Price, Rogers, and Young succeeded in banishing the disease in parts of Assam. Good results in prophylaxis have already followed the actual treatment of cases on a large scale. Energetic measures against sandflies should be instigated (*see* p. 179). This involves protection against sandfly bites and the control of sandfly breeding places.

II. ORIENTAL SORE

Synonyms. Tropical Sore; Bouton d'Orient; Delhi Boil; Cutaneous Leishmaniasis; Bouton de Biskra; Bouton de Bagdad; Aleppo Boil; Salek (Persia); Pendeh Sore (Southern Russia).

Definition.—A specific ulcerating granuloma of the skin, endemic within certain limited areas in many warm countries. It is caused by *Leishmania tropica*. and is characterized by an initial papule which, after scaling and crusting over, generally breaks down into a slowly extending and very indolent ulcer. Healing after many months, it leaves a depressed scar. The sore is inoculable and, usually, protective against recurrence.

History.—In 1885 Cunningham first described certain deeply-staining parasitic bodies in mononuclear cells derived from these sores. Hoare pointed out that it was Borovsky (1898), a military surgeon stationed at Tashkent, who first accurately described *Leishmania tropica*, and later (1902) Shulgin concluded that some night-biting insect was the intermediary host. J. H. Wright in 1903, ignorant of Borovsky's work at that time, named the bodies *Helcosoma tropicum*. These observations have been abundantly confirmed, and the parasite is regarded as identical with the Leishman-Donovan body, and is known as *Leishmania tropica*. In 1907 Marzinowsky inoculated himself in Moscow with material obtained in the Caucasus, and reproduced a typical sore on his forearm.

Geographical and seasonal distribution.—Oriental sore occurs in Italy, where Vanni (1938) has recorded 300 cases in Abruzzi; Morocco; the Sahara (Biskra, Gafsa); Egypt (Zagazig and Minia, in the Nile Delta); Crete; Cyprus; Sicily; Asia Minor; Syria (Aleppo); Palestine (Jericho); the Sudan; Nigeria; Iraq (Bagdad); Arabia; Persia; the Caucasus; India (Lahore, Multan, Delhi, Dera-Ismail-Khan, etc.); the Transcaspian Provinces; Turkestan (Tashkent and Bokhara); China, especially in Hunan. In South and Central America it is often, but not invariably, found in association with naso-pharyngeal leishmaniasis, especially in Peru, Bolivia, Brazil, the Guianas, and Mexico (Map III).

In the tropics it is especially prevalent about the beginning of the cool season; in more temperate climates, towards the end of summer or early autumn. Years of prevalence may be succeeded by years of comparative rarity—possibly in harmony with altered sanitary conditions. In Delhi, for example, in 1864, from 40 to 70 per cent. of the resident Europeans were affected with the local sore; when certain sanitary improvements were made, the frequency of the disease was immediately materially reduced.

Epidemiology and endemiology.—Although oriental sore may occur in countries where kala-azar is endemic, its distribution is as a rule quite distinct (*see* Map III). In India cutaneous leishmaniasis is confined to the west, whereas kala-azar is endemic on the east coast. In North Africa, oriental sore occurs north of latitude 35°, whereas kala-azar is found south of this line. In Persia and Iraq, where oriental sore is very common, kala-azar is absent. Central Asia is an exception for, according to Gerschenowitsch, they are found side by side, even in a single family, and both diseases have been seen in the same patient. Apparently also, recovery from cutaneous infection does not necessarily protect against subsequent infection by the kala-azar parasite. Oriental sore and kala-azar are found together in the Southern Sudan and also in Crete (*see* p. 153), where, according to Adler, their respective carriers, *Phlebotomus sergenti* and *P. major*, are both present.

In the endemic areas, oriental sore appears to have a seasonal preference, making its appearance in the dry season between September and January, in cities like Aleppo and Bagdad, where the disease is very common. In Turkmenistan the maximal incidence is æstivo-autumnal. Children usually acquire it between 2 and 3 years of age, and natives rarely attain maturity without having had one or more sores. In fact, it may be said that every woman in Bagdad bears on her face marks of the ravages of this disease and for centuries it has been the custom there to inoculate children to prevent infection in later life.

In Turkmenistan Russian workers recognize two types : rural and urban. In the former the infection is said to be derived from animal reservoirs (gerbilles) ; in the latter from human sources.

Oriental sore occurs as a natural disease in dogs and cats. The organism has been demonstrated in cutaneous sores on the ears, lips, nose and inner canthus of the eye of these animals in Teheran, Tashkent, Iraq (where it is only seen during the winter months) (Machattie, Mills and Chadwick), and recently in South America and India ; while Sinton has shown that the leishmania sores occurring in the noses of dogs in India are transmissible to man. *Macaca* monkeys are easily inoculated. Oriental sore has been found as a natural infection of the brown bear and bullock in Turkmenistan, and also on the nose of a horse by Bennett in Kordofan. Natural infections in a gerbille (*Rhombomys opimus*) have been reported from Turkmenistan, and are said to be common. An allied form (*L. myoxi*) occurs in the dormouse.

Ætiology.—The causative parasite—*Leishmania tropica*—is found in numbers in the granulating tissue at the edge of the lesion and may be demonstrated in scrapings. They frequently occur in rosettes, often enclosed in macrophage cells or in leucocytes. *L. tropica* resembles *L. donovani* in its morphology and behaviour, and in culture on N.N.N. medium. To collect material for cultivation the surface of a non-ulcerating sore is painted with iodine, and the edge is then punctured with a fine glass pipette. Like *L. donovani*, the parasites grow best in the water of condensation. In heavy infections the flagellate—*leptomonas*—forms appear within forty-eight hours. Then the parasites undergo identically the same changes as do *L. donovani*, but they are able to flourish in conjunction with contaminating micrococci, which the leishmania of kala-azar cannot do.

Noguchi once made the interesting observation that the addition of immune serum from an experimentally inoculated rabbit causes the organisms to develop in clumps. In Syrian hamsters, and occasionally in mice, *L. tropica* produces generalized visceral leishmaniasis. Monkeys, dogs, mice and Syrian hamsters are experimentally inoculable, whilst donkeys, goats and sheep are refractory. In man a certain degree of immunity is produced so that, as a rule, second attacks of oriental sore do not occur.

Senekji and Beattie inoculated a large number of volunteers in Bagdad with cultural forms of *L. tropica*, and reproduced sores in the great majority. Subsequent attempts at reinoculation were unsuccessful.

Transmission.—Wenyon (1911) first suggested the sandfly (*Phlebotomus*) as the vector in Bagdad, and found that 6 per cent. of these insects in Aleppo harboured a flagellate of the *Leptomonas* type in their intestines. Later, further confirmatory evidence was brought forward by the Sergents, Parrot, Donatien, and Béguet (1921), who produced oriental sores in Algiers after scarifying the skin and applying a saline suspension of crushed *P. papatasii*. The incubation period was two and a half months. These sandflies were caught in Biskra, where oriental sore is common, and transported 600 kilometres to Algiers, where the disease does not occur. Later still, Adler and Theodor repeated these experiments with a *Herpetomonas*, which is a natural infection of *P. papatasii*. The development of *L. tropica* in the body of the sandfly follows that already described for *L. donovani*. Adler and Theodor have strikingly confirmed this, and have produced infection of *P. papatasii* by feeding these sandflies through a membrane on emulsions of leishmania.

The vector in North Africa and the Eastern Mediterranean is *P. papatasii*; in Crete, Iraq, India and Persia *P. sergenti*; and in Central Asia *P. caucasicus*. In Italy, according to Vanni, *P. perfiliewi* (*macedonicus*) is the chief carrier.

Monkeys, dogs, mice, and Syrian hamsters have proved to be experimentally inoculable, while donkeys, goats, and sheep are refractory. In Syrian hamsters, and occasionally in mice, inoculation of *L. tropica* produces a generalized visceral leishmaniasis.

Pathology.—There is continuous progression of cellular changes, so much so that a section taken at any particular time cannot give a complete picture of the processes involved. In the early stages there is proliferation consisting almost entirely of reticular cells, which form a syncitium. This proliferation may be so dense as to interfere with nutrition of the epidermis, and the proliferating reticulum is packed with parasites. Later, there is an invasion of lymphocytes, plasma cells and large mononuclears, and occasionally giant cells, accompanied by a considerable diminution of parasites. It may, therefore, be regarded as part of a protective mechanism, albeit not a very successful one, because the lesion, though now containing relatively few parasites, may still persist for months. Gradually, the lesion is replaced by scar tissue. In some cases parasites are very scanty in all stages of the lesion and, in these, there is local infiltration of lymphocytes, plasma and giant cells from the beginning. The histological, as well as the clinical picture may resemble lupus very closely.

Immunity.—A considerable degree of immunity is produced by repeated infection with oriental sore, which eventually becomes absolute—a fact which has been well recognized in Bagdad. On experimental grounds this was proved by Laveran, who found that repeated inoculation produced immunity in experimentally-infected dogs.

Incubation period.—The incubation period of oriental sore is variously stated in days, weeks, or months. That it may be a brief one, a few days or weeks, seems to be established by the appearance of the sore within a short time of arrival in endemic districts, or after inoculation. That it can be of much longer duration is equally certain. Manson saw an unquestionable oriental sore which did not appear until five months after the patient had been exposed to any possibility of infection. Wenyon inoculated himself with oriental sore in Aleppo; it was not until six and a half months later that a leishmania-containing papule, subsequently developing into a sore, appeared at the site of inoculation. In some cases the incubation period appears to be as much as fifteen months, or even longer. Sometimes eruption of the sores is accompanied by fever and other constitutional symptoms, and temperatures up to 103° F. have occasionally been noted.

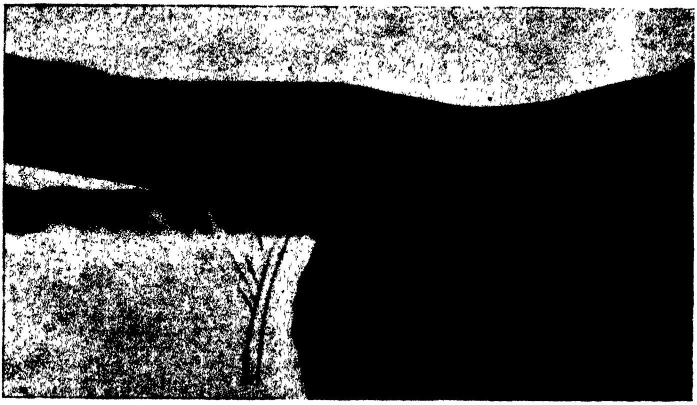


Fig. 26.—Papular dermal leishmaniasis with depigmentation in a Singapore Indian.
(*Dr. B. Hawes*)

Symptoms.—The local lesion in oriental sore commences as a minute itching papule which tends to expand somewhat as a shotty, congested infiltration of the derma (Fig. 26). After a few days or weeks the surface of the papule becomes covered with fine, papery scales. At first these scales are dry and white; later they are moister, thicker, browner, and adherent. In this way, a crust is formed which, on falling off, or on being scratched off, uncovers a shallow ulcer (Fig. 27). The sore now slowly extends, discharging a scanty ichorous material; this from time to time may become inspissated, and a crust forms, while the sore continues to spread underneath. The ulcer extends by the erosion of its perpendicular, sharp-cut and jagged edge, which is surrounded by an areola of congestion. Subsidiary sores may arise around the parent ulcer, into which they ultimately merge. These sores, usually about an inch in diameter, may come, in some instances, to occupy an area several inches across.

After a variable period, ranging from two or three to twelve or even more months, healing sets in. Granulation is slow and frequently interrupted. Often it commences at the centre while the ulcer may be still extending at the edge ; often it is effected under a crust. Ultimately, a depressed white or pinkish cicatrix is formed. Contraction of the scar may cause considerable and unsightly deformity. Thus, on the face, scar tissue may produce retraction of the external canthus (epiphora), deformity of the naso-labial folds or eversion of the angle of the mouth.

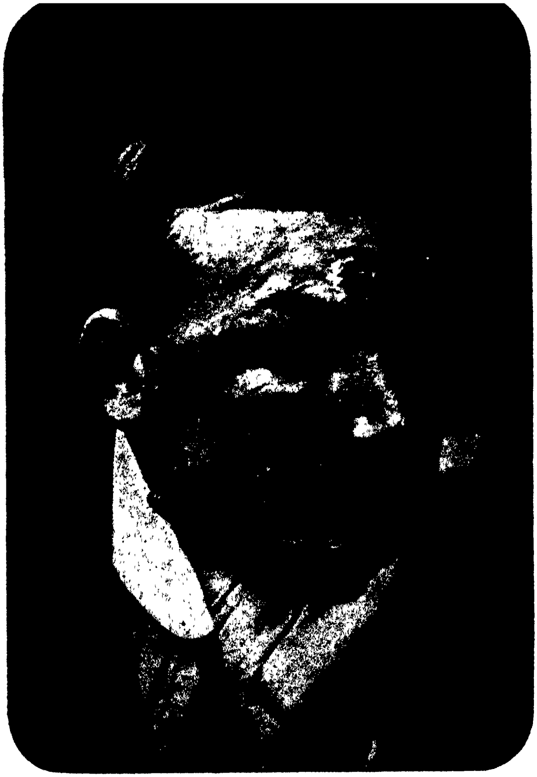


Fig. 27.—Oriental sore. (*After Wenyon. Photo : R. McKay, reproduced in "Journ. Lond. School Trop. Med."*)

Oriental sore may be single or multiple (Fig. 28). Two or three sores are not uncommon ; in rare instances as many as one hundred and fifty have been counted on the same patient. They are mostly situated on uncovered parts—hands, feet, arms, legs and, especially in young children, on the face ; rarely on the trunk ; never on the palms, soles, or hairy scalp. Occasionally these ulcers may occur on the ears, tip of the nose, lower lip, and even on the tongue (Hawes, Panja, Dastidar, Trifilo). This seems to be more frequent than had been supposed, and provides a link between the Old and New World leishmaniasis. A small multiple diffuse form may resemble diffuse papillomata : very rarely they occur on the buttocks or on the perineum. The Editor investigated a case with

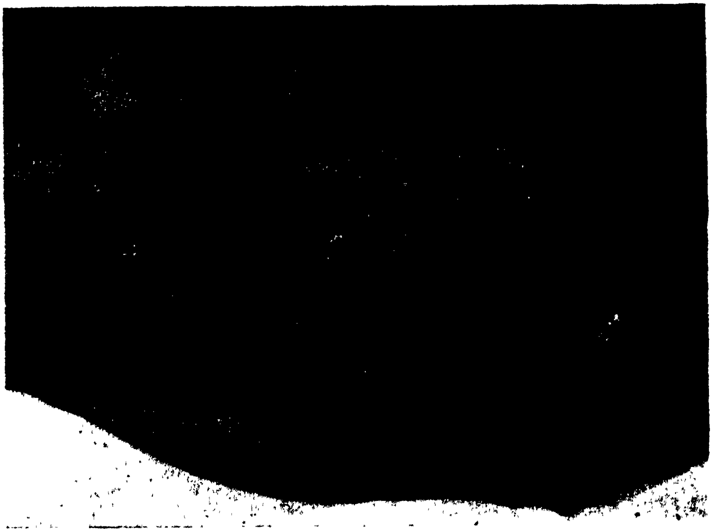


Fig. 28.—Diffuse cutaneous leishmanial lesions on arm. (*After Byron*

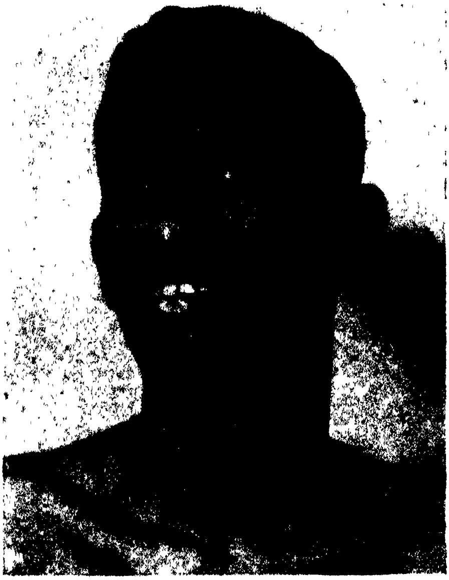


Fig. 29.—Nodules on nose and lip in Indian Tamil with cutaneous leishmaniasis.
(*Dr. B. Hawes.*)

Mr. P. Lockhart-Mummery in which a diffuse indurated swelling close to the anus was found to contain large numbers of *L. tropica*.[1]

In a very few instances the initial papule does not proceed to ulceration, but persists as a scaling or scabbing, non-ulcerating, flattened plaque—just as sometimes happens in the primary sore of syphilis. Sometimes the ulcer is quite superficial, an erosion rather than an ulcer. Occasionally, from contamination with the organism of some other infectious acute inflammatory skin disease, the primary lesion may become complicated, and perhaps a source of serious danger. Otherwise, oriental sore is troublesome and unsightly, rather than painful or dangerous. When ulcerated, or secondarily infected, the neighbouring lymphatic glands in the area of the sore may be enlarged.

Associated subcutaneous nodules have frequently been described (Fig. 29). Thus, Byron Evans (1938), in a case of extensive cutaneous leishmaniasis, found, around the arm lesions, five separate apple-jelly-like papules. Others were seen around similar lesions on the opposite arm or leg. In size they varied from 0·25 to 1 cm. in diameter ; they were firm, discrete and freely movable and were not tender. On removal, they showed chronic inflammation with fibrosis, and Leishman-Donovan bodies, suggesting a chronic lymphatic infection with leishmania and denoting the spread of the infection *via* the lymphatic route. Lymphatic nodules were described as early as 1847 by Poggioli and by Bonne (1901), also, in association with South American leishmaniasis, by Darier, de Christmas, Escomel and Werner.

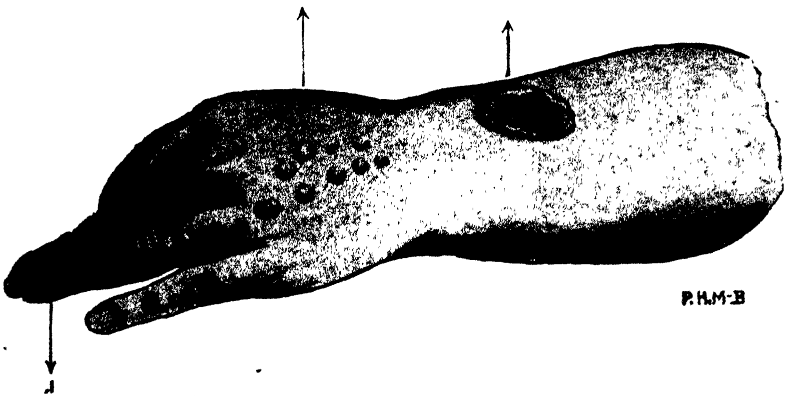


Fig. 30.—Lymphatic spread of oriental sore.
1, Primary sore on finger ; 2, secondary crateriform sore on wrist ; 3, nodules in course of lymphatics.

In Christopherson's case (1923) there were twenty-five vesicular lumps of varying sizes which contained leishmania, while the Editor found similar swellings on the dorsum of the hand and over the submental gland in his patient (Fig. 30). Gonzalez, Boggino and Rivarola described a similar case in 1937. A sharp bout of pyrexia (T. 103–104° F.) frequently precedes the appearance of the nodules.

---

[1] The Russians (Kojeynikov *et al.*) now recognize two types :—the *dry* prolonged incubation period, of which the reservoir is man, and the *moist*, or rural, period and lymphangitis, in which wild rodents (gerbilles) constitute the reservoir.

Nodular or verrucose form.—A peculiar kind of dermal leishmaniasis, or parasitic granuloma, has been described by Ferguson and Richards in Egypt (Fig. 81). These lesions, which usually affect the lower extremities, resemble warty out-growths or papules; they may be solitary or multiple, and may be the result of auto-inoculation. They are best treated by excision.

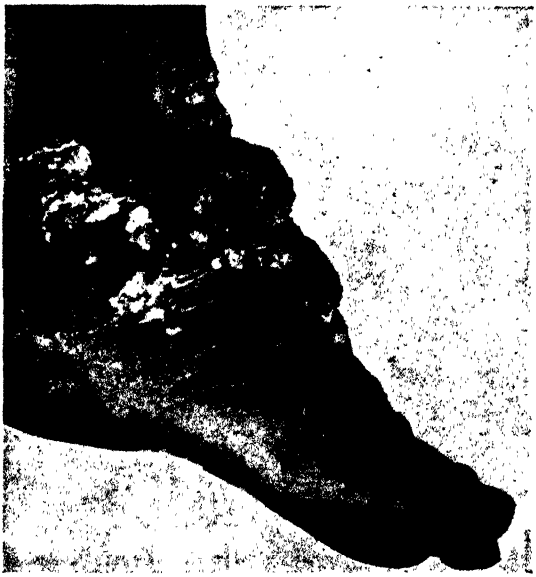


Fig. 81.—Diffuse cutaneous leishmaniasis of the leg in an Egyptian.
(*Ferguson and Richards. By permission of Liverpool School of Trop. Med.*)

recidiva.—The relapsing tuberculoid form, involving large areas of skin, especially of the face, is an allergic manifestation and therefore analogous to cutaneous tuberculides, closely resembling lupus vulgaris. It is known as leishmaniasis recidiva. Only with great difficulty can Leishman-Donovan bodies be recognized in preparations, but they can usually be isolated by culture. Relapses occur after the original lesion heals and often take the form of nodules and papules, situated at the periphery of the scar. Christopherson originally described lupus-like nodules on the cheek, and also recognized a keloid form. Leishmaniasis recidiva is resistant to all forms of treatment except the Grenz rays.

Generalized non-ulcerating form (dermal leishmanoid).—Brahmachari described papillomatous nodules over the whole of the body, due to Leishman-Donovan bodies, which at first were thought to be tubercular leprosy (*see* p. 159), but all cases had previously been treated for kala-azar, and had apparently recovered after antimony injections.

infections.—Superadded staphylococcal or streptococcal infections are common. Secondary diphtheritic and streptothrical infections have been described.

Diagnosis.—On clinical grounds these sores have to be distinguished from the desert or veld sore (p. 642), tertiary syphilis, ulcus tropicum, lupus vulgaris, and blastomycosis. The distribution of the sores and the presence of the Leishman-Donovan body render the diagnosis a matter of no very great difficulty. The parasites are best demonstrated by sterilizing the skin at the edge of the ulcer, and running in a fine glass pipette through a puncture made in the skin, to get beneath the ulcer, and obtain serum and tissue cells—but not blood—if possible free from bacterial contamination. This is a better method than scraping the surface of the ulcer with a blunt needle or with a fine knife. If parasites cannot be found, cultures should always be made. Additional help may be obtained by the *leishmanin test:* the intradermal injection of 0·1 c.c. of a suspension of flagellates in culture (1,000,000 per c.c.). A specific reaction is produced in active, as well as in healed oriental sore lesions. Care must be taken to distinguish the Leishman-Donovan bodies from yeast cells, which are sometimes present in cutaneous ulcers and may simulate them.

The aldehyde test is negative.

In leishmaniasis recidiva differential diagnosis has to be made from tuberculides of the hypoderm, including Bazin's disease. Adler insists that the apple-jelly nodules so closely resemble lupus that cultures on NNN medium should always be made (Fig. 32).

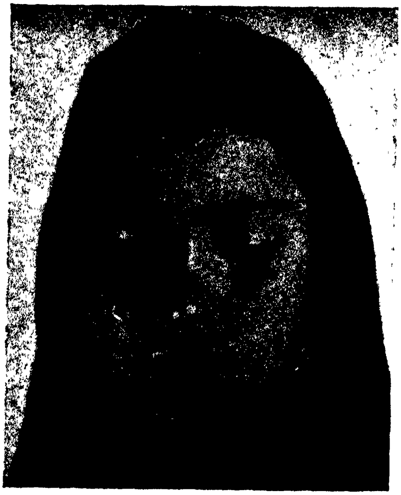


Fig. 32.—Cutaneous leishmaniasis in Egyptian girl. Lupus-like "apple-jelly" nodules.
(*Dr. H. K. Giffen, Assiut.*)

TREATMENT

The treatment of oriental sores in general, especially in a temperate climate, does not, as a rule, entail any particular difficulties, for the reaction of the tissues to the particularly indolent ulceration depends to some extent upon the general nutrition and environmental conditions. When the patient is removed from the endemic area, the disease tends to disappear spontaneously in about one year.

(*a*) **General measures.**—When the sores are multiple, as they so often are, and when they are situated on the extremities, undoubtedly the best treatment is intravenous injections of antimony, especially the pentavalent compounds (p. 165). Antimony tartrate (sodium antimony tartrate) is efficacious in 2 per cent. solution, and the total amount necessary is, as a rule, 15 gr. (1 grm.). Of the pentavalent preparations, *Neostibosan* or *Neostam* are equally suitable and, when feasible, should be given intravenously in doses commencing with 0·1 grm. and increasing on alternate days to 0·3 and 0·4 grm. Much smaller total quantities (1–2 grm.) effect a cure than in kala-azar. For women and children, to whom injections cannot be given intravenously, the intramuscular route should be chosen (*see* p. 165). Raymond and Cruickshank, in an account of an epidemic of these sores following the Quetta earthquake, found injection of trivalent antimony compounds (tartar emetic and fouadin) combined with local scraping the most effective method. Pentavalent antimony preparations were less satisfactory under these conditions.

(*b*) **Local measures.**—Intravenous injections of antimony do not act so well for sores situated on the face—eyebrows, nose, cheeks, lips—and hands, which tend to be chronic, indurated, and subject to secondary infection.

Secondary infection is a most important element and in these cases no treatment is of any avail until the scabs have been removed and the sepsis cured by hot fomentations, eusol dressings, and nitrate of mercury ointment. Recently, however, powdered sulphapyridine has proved beneficial (Akrawi).

Ointments.—Various applications have been found useful on different occasions, *e.g.* *Cignolin* (a refined product of chrysophanic acid), in the following formula :

℞	Cignolin	gr. iv	(0·259 grm.)
	Ichthyol	gr. viii	(0·518 grm.)
	Ol. cadini	♏ xl	(2·368 c.c.)
	Benzoli rect. ad	℥i	(28·42 c.c.)

Ft. pigmentum : To be applied to sore every day.

This paint should be applied to the sore with a camel-hair brush, care being taken not to overlap on to the surrounding skin, daily for 2–4 weeks, after the sores have been cleaned up with eusol dressings or boric fomentations. This treatment is especially applicable to sores on the face in children, and the Editor has had striking and favourable results.

Other ointments which have been recommended are : *Pellidol* (Bayer), containing 2 per cent. diacetylamine-azol-toluol, *Desitin* (Klinke) (chlorine and cod-liver-oil salve), and *Orisol* ointment, which contains berberine sulphate. Good results have been reported from the local application of phosphorated oil, and also from finely-powdered permanganate of potash. The local application of vanadium in a preparation " Tarvan " is said to be a very active remedy (Pereira). Kassirsky, in Tashkent, has found effective an ointment prepared from the whole seeds of *Ricinus* (of which the active principle is ricin), ground up and mixed with 10 per cent. vaseline ointment. It is applied every few days to the ulcer ; the first applications cause considerable irritation.

Injections into the base of the sores.—These methods of treatment probably act by causing a tissue reaction but, as a rule, injections are painful and, on account of the surrounding inflammation, cannot be used for sores on the face, especially near the eyes.

Treatment by injection of emetine.—Photinos reported good results from local injections of emetine hydrochloride, and Sinderson in Iraq used a 2 per cent. solution injected so as to reach every part of the sore, so that in large ulcerations it may be necessary to puncture in three or four places. The needle of the syringe is inserted into the healthy skin and passed through the tissues. The solution is injected, the needle being gradually withdrawn at the same time. After the injection the puncture site is sealed with cotton-wool and collodion flexile. When ulceration is deep, healing may not be complete for a month. A local inflammation is set up, and the parasites disappear from the lesion. The lesions usually clear up in fifteen to thirty days.

Injections of berberine sulphate.—Subcutaneous injections of berberine sulphate (Karamchandani) have been used extensively in India. A quarter of a grain is dissolved in 1·5 c.c. of distilled water and injected at four or more points round the sore. Two to four injections, when combined with dressings of hypertonic saline, usually suffice. The solutions are very stable and can be preserved in sterile tubes with rubber caps. Hamilton Browne and Deri state that, if the sore is not healed within a week, treatment must be repeated, but a third course is rarely necessary.

Treatment of indolent sores on the nose.—These require special mention as, on account of the induration of the surrounding tissues, they are especially refractory and they do not appear to respond to the applications which are efficacious in other situations. After being cleansed, the bases should be scraped by a Volkmann's spoon and dilute nitrate of mercury ointment thoroughly rubbed it. Dry dressings and sulphonamide paste should subsequently be applied.

Treatment by vaccines made from dead cultures of *Leishmania* has been successfully practised by Schwartzmann, Chodukin, and others. The vaccine consists of a saline suspension of washed flagellates killed by heat.

X-ray therapy.—In Iraq it is stated that a single full-pastille dose of X-rays produces a cure within ten days in the majority of cases. The rays probably cause acceleration of the protective processes and infiltration of leucocytes into the base of the sores. An X-ray set capable of operating continuously at a voltage of 100–120 K.V. and 2–4 m.A. is suitable for the purpose. A filter of 0·5 mm. of aluminium is used at a focal skin distance (F.S.D.) of 23–25 cm. A total dosage of 450–1,000 " r " units is given, either in one dose or in two smaller doses at intervals of 10 days. (One erythema skin dose (E.S.D. = 450 " r " = one pastille dose).

Soft Grenz, or Bucky rays.—These are half-way between ultra-violet and X-rays. This form of treatment has been described by Dostrovsky and Sagher (1942). It has the special advantage that lesions overlying sensitive organs (eyelids, thyroid gland and genital organs) and the growing organs of children can be treated. Leishmaniasis recidiva has proved refractory to every form of therapy but this. The nodular and verrucose forms are especially amenable. The total dose employed for the latter is two exposures of 800 r with half value layer of 0·027 mm. aluminium, whilst for leishmaniasis recidiva the total is from 3,000–11,000 r with half value layer 90·02 mm. aluminium. The nodular type of lesion disappears in eight weeks, but with the relapsing form treatment may be spread over six to eight months.

Treatment by ionization.—This has given satisfactory results. The ulcer is cleaned and covered with a pad consisting of sixteen layers of lint soaked in 2 per cent. zinc-sulphate solution; this is firmly applied under a zinc electrode by a bandage, and then connected with the positive pole of an electric current which is supplied by eighteen accumulators giving an average of 36–38 volts. A patient with a sore of an area of 1 in. in diameter can easily stand 10 ma. as gauged by a resistance coil. The application is continued for twenty minutes, the pad being constantly moistened with zinc-sulphate solution.

Treatment by carbon-dioxide snow.—The application of carbon-dioxide snow has been recommended for 5–30 secs., depending upon the size of the lesions; it should be repeated every ten days.

Prophylaxis.—In the endemic areas insect repellents (*see* p. 115) should be used to protect the exposed parts against bites of *Phlebotomus*. At night-time a fine-mesh netting, forty-five holes to the square inch, is necessary to exclude these insects (*see* Fig. 12). Dogs with suspicious-looking sores should not be permitted near dwellings. Prophylactic inoculation with cultures of *Leishmania tropica* has been practised in south-east Russia (Lawrow and Dubowskoj). Sores develop at the site of inoculation after an incubation period of two to six months. The immunity thus produced protects against further infection.

III. LEISHMANIASIS AMERICANA

Synonyms. Espundia; Bubas Braziliana; Uta; Pian Bois; Forest Yaws (British Guiana); Bosch Yaws; Naso-pharyngeal Leishmaniasis.

History.—Under these names several writers describe a very grave form of leishmaniasis in certain South American countries; isolated cases resembling the American disease have been reported from the Sudan (Christopherson, Humphreys, Mayne and Kirk), Somaliland and Italy, but possibly in these it merely represents a secondary invasion of the mucous membranes from the surrounding skin. Mutilations of the face reminiscent of this disease have been found in figures engraved on old Inca pottery.

Geographical distribution and epidemiology.—The most northerly point from which this form of leishmaniasis has been reported is the Peninsula of Yucatan, about 21° north latitude, and the most southerly 30° south in the Argentine. It is prevalent in the northern part of Argentina and in Paraguay at 25° south. Probably the centres of its greatest prevalence are in the states of São Paulo, Bahia in Brazil, and in parts of Peru between 5° and 25° south. Altitude is a limiting factor. Most of the territory has an elevation of less than 2,000 feet. Heat and moisture are necessary for its existence. In the chicle (gum) forests of Yucatan the infection is contracted in the rainy season.

In highly endemic areas the majority of cases occur after six months residence, especially in the autumn. The prevalence of disease is definitely related to the density of the sandflies which transmit it.

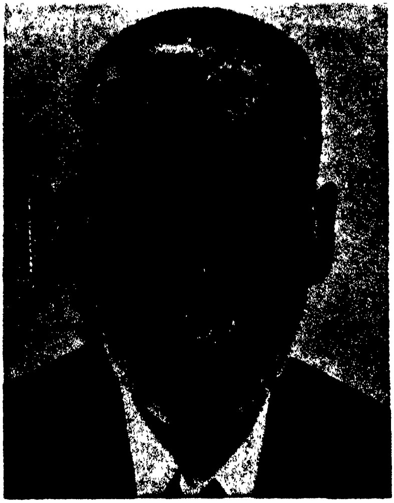


Fig. 33. — Leishmaniasis Americana affecting the nose and upper lip. (*Bernasconi and* [illegible])

In Rio de Janeiro, however, the disease is common in the residential section. It has also been reported from the West Indies (Martinique), Mexico (State of Campeche), and Yucatan, British Honduras, Honduras, Guatemala, Colombia, British, Dutch and French Guiana, Uruguay, Bolivia and Ecuador (Map III). Occasional somewhat similar cases have been recorded in the Sudan, Italy, India and China.

In Paraguay the disease has assumed epidemic characters, and a large proportion of the population in certain districts, and 70–80 per cent. of prospecting parties, have become affected, so that most drastic public measures have had to be taken to prevent its spread. It is usually seen in men working in the forests, especially gum-pickers. A similar disease has been observed in the dog in the endemic centres, and it is possible that it occurs in the agouti (*Dasyprocta*). Pestana, Villela and co-workers working on the epidemiology of this disease in São Paulo, Brazil, concluded that intimate contact with wooded country is not always necessary. It is usually rural in distribution, but has been seen in some towns. In Minaes Geraes, Brazil, this form of leishmaniasis is becoming increasingly important, and its incidence is very high. The duration of the disease is from four months to four years. In the majority there are mixed mucosal and cutaneous lesions.

Ætiology and symptoms.—The disease occurs at any age in either sex, in strangers as well as in the indigenous population. São Paulo seems to be an exception, as Villela says it is there nine times more common in men than in women. It begins as a sore on some mucous surface. The sore is of the chancrous form of the ordinary oriental-sore type. It heals in time, leaving a characteristic scar. After an interval of months or years, most intractable fungating and eroding ulcers (Fig. 33) break out on the tongue, and in the buccal and nasal cavities, destroying and obstructing them, and ultimately, if untreated, leading to death by exhaustion after years of suffering. The lymphatic glands are often involved, but the abdominal and thoracic organs are spared. Though affecting the mucous membranes in this characteristic manner in the endemic zones, the ulcers, as in oriental sore, occur in other uncovered parts of the body. They have been commonly noted as lupus-like lesions on the pinna of the ear in gum-pickers (*oreja de chicleros*). For the state of São Paulo, Brumpt and Pedroso record localization of sores as follows (in percentages): Leg 30, foot 12, forearm 12, head 11, hand 10, hip 4, elbow 4, trunk 3, nasal mucosa 3, knee 2, buccal mucosa 2, neck 2, arm 1, pubes 1.

Leishman bodies are found, though not in great profusion, in scrapings and sections of the fungating ulcers, and present no morphological differences from *L. tropica* or *L. donovani*, but have been separated by Vianna as *Leishmania braziliensis*. The parasites can be cultivated in the same manner as *L. tropica* and on the same media, but Geiman showed that *L. braziliensis* grown on the chorio-allantoic membrane of the chick embryo shows much poorer infectivity than *L. tropica*. Giant cells and flagellated forms of the parasite have been found in sections. It is believed that the original sore in this grave form of leishmaniasis develops at the site of the bite of a jungle insect, probably a sandfly—*Phlebotomus*—and the following species are suspected (Shattuck, 1935): *P.*

(Dutch Guiana and Brazil); *P. intermedius* (Brazil and Argentina); *P. migonei* (Venezuela, Brazil, Paraguay and Argentina).

These sores infiltrate deeply into the tissues, and, besides grave destruction of the nose, lips, and tongue, they may be followed by secondary infections, such as erysipelas and even gangrene.

Diagnosis is made upon the typical clinical appearances and the discovery of the parasite. Espundia has to be distinguished from the ulceration of yaws (gangosa), lupus and syphilis. In ulcerated lesions the crust should be removed and smears made from the underlying seropurulent discharge.

The excision of a piece of granulation tissue and the expression of the contained serum on a slide often afford a more ready diagnosis. In five cases discovered in the Sudan, Humphreys and Mayne found the leishmania in material obtained by pinching the lobulated growths, but not by splenic puncture. The intradermal (*leishmanin*) test of Montenegro consists of an extract of flagellates (on culture) washed in physiological saline solution containing 0·4 per cent. phenol. This can be kept for long periods in the ice-chest. Gomes found it was moderately positive in 97·5 per cent. of South American cutaneous leishmaniasis.

The exact relationship of the mucosal leishmaniasis in the Sudan to espundia is not easy to determine. The South American disease has a specific course of evolution and occurs in epidemic form, which is not the case in the Sudan, where oro-nasal leishmaniasis is relatively uncommon. In the nose the nasal septum and alæ nasi may be involved, whilst localized swelling occurs on the lower lip. In almost every instance there, evidence of a concomitant visceral infection has been noted.

Treatment.—The general treatment is the same as for oriental sore, and was introduced by Vianna in 1912; ten to twenty intravenous injections of antimony tartrate (20–30 gr.) or of the pentavalent compound, neostibosan, suffice for cure. The local ulcers on the lips and nose are cleaned up with fomentations, the cleansed surfaces anæsthetized with a mixture of cocaine, menthol, and carbolic acid, then sprinkled with finely powdered antimony tartrate and bound up with a bandage. Subsequently the wounds are dressed with an ointment composed of zinc oxide, bismuth, and lanolin. From the buccal mucosa scabs must be removed with a solution of bicarbonate of soda, the surface anæsthetized with cocaine (1 per cent.) and sprayed with 1–2 per cent. antimony tartrate solution. Every four to eight days the tartrate is used in a saturated solution, the application being made on a pledget of cotton-wool.

Mazza and others in northern Argentina had good results with intramuscular injections of *Fouadin* (or stibophen), a trivalent antimony compound, in doses varying from 0·5 to 5 c.c. The treatment was continued for varying periods. Twenty to thirty injections are usually necessary and, according to Schulemann, the results continue to be satisfactory.

Good results more recently were obtained by intramuscular injections of *Eparseno* (dioxy-diamido-arsenobenzol), prepared by Poulenc Frères, Paris. Injections of 0·12 to 0·25 grm. (1–2 c.c.) are given and as many as 10–20 injections at intervals of two to three days are necessary. Others obtained success with similar injections of the double iodide of quinine and bismuth (0·15 grm. daily for one month). Atebrin (mepacrine hydrochloride) injections are advocated by Mazza and Cornejo in isolated sores: 5 c.c. of a 10 per cent. solution is injected into the base of the sore and three tablets given by the mouth for seven days.

In assessing the relative value of the various treatments, it must be remembered that spontaneous cure appears to take place in about 7 per cent. of cases (Pessoa).

Subsection B.—FEVERS CAUSED BY BLOOD SPIROCHÆTES AND SPIRILLA

CHAPTER VI

RELAPSING FEVERS

Synonyms. Febris Recurrens; Spirillum Fever; Famine Fever; Tick Fever; Bilious Typhoid of Griesinger.

Definition.—A group of diseases, characterized by fever of sudden onset and, after several days (one to seven), rapid subsidence, which may relapse at intervals of from one to seven or more days for an indefinite number of times. They are caused by spirochætes, which are present in the blood during the fever and are transmitted by the body-louse (*Pediculus*) or by certain ticks (*Ornithodorus*).

History.—Relapsing fever was known to Hippocrates. In 1873 Obermeier discovered the spirochæte now known as *recurrentis*, vel *obermeieri*. In 1904 Philip Ross and Milne in Uganda, and rather later, but independently, Dutton and Todd on the Congo, found that in Africa the local spirochæte was communicated by the bite of a tick, *Ornithodorus moubata*. They found also that the parasite could pass into the egg and larva, and so confer infective powers on the tick of the succeeding generation. In 1907 Mackie recorded an outbreak of relapsing fever in which lice, *Pediculus humanus* var. *corporis* and *capitis*, apparently served as the transmitting agents—a view favoured by the experiments of Nicolle and others. In 1921 Bates, Dunn, and St. John proved that, under experimental conditions, the ticks *Ornithodorus talaje* and *O. venezuelensis* convey the disease in Panama and in Venezuela. A Spanish form described by de Buen occurs in Southern Spain and Morocco and is transmitted by *O. marocanus*, which lives mostly in the burrows of rats and porcupines and the earths of foxes, and also frequents pigsties. Since then Herms has described a distinctive tick-borne form in California, and Adler a similar ornithodorus-conveyed disease in Palestine.

Geographical distribution.—In Europe relapsing fever occurs from time to time in the British Isles, especially in Ireland, and in Norway, Denmark, Germany, Russia, and Turkey. In Africa the disease has long been known in Egypt, while Dutton and others found a specially virulent form widely spread in Central Africa (tick fever) in the Congo, East Africa, Uganda, Abyssinia, and Madagascar. Ordman recently reported an epidemic in Cape Province, South Africa. In Asia it is met in Persia, and in India, where in 1922 large epidemics occurred in the Central Provinces and North-Western Frontier. Epidemics have been recorded in the United States, especially in Texas. An extensive and virulent epidemic, associated with intense jaundice, commenced in 1921 in North Equatorial Africa and spread across the Continent south of the Sahara at about 15° N., and continued for over seven years. Eventually it reached the Atlantic in Senegal and the Gold Coast, and thence extended through Upper Guinea, French Niger, Nigeria, Lake Chad, Wadai, and Western Egyptian Sudan. The louse-borne form is common in China and Manchuria. A special tick-borne form of the disease is recognized in

California, as well as in the northern states of Central and South America, Spain, Morocco, Palestine, Turkmenistan, Syria, and Persia.

Ætiology.—The various clinical forms of relapsing fever are caused by *Spirochæta recurrentis*, or organisms which are morphologically indistinguishable from it but which may be biologically separable, such as *S. duttoni* and *S. venezuelensis*.

Typically, the spirochæte is a delicate spiral filament; its length varies from 8 to 15 μ, and its width from 0·2 μ to 0·3 μ. Each turn has an amplitude of 2 to 3 μ. The body of the parasite may have three, four, or six bends or turns; dividing forms appear to have more; in fact, the body of the spirochæte undulates, it does not strictly form a spiral. Coles describes the minute structure as consisting of small granules in a containing tube. By the Romanowsky method the body of the parasite usually stains uniformly, with the exception of the extremities, which are pointed and take only a very faint tint. In fresh blood the spirochætes exhibit very active screw-like movement; some are longer than others, the long forms resulting from end-to-end attachment of two or more parasites. That this is the explanation of the long forms, which may measure from 16 to 100 μ, is shown by staining. In those measuring from 16 to 18 μ we find a pointed extremity at each end of the filament and a pale zone in the middle, the pale zone corresponding to the approximated lightly staining extremities. The still longer forms admit a similar explanation. Although the normal habitat of the spirochætes is the liquor sanguinis, occasionally in fresh liquid blood preparations they are seen within the red blood-corpuscles, though this probably does not occur within the body.

Great variation is shown in morphology, but there is a consensus of opinion now that no constant distinctions exist between the organisms in the different clinical forms of the disease. For an explanation of the nomenclature the reader is referred to p. 185.

Demonstration of the spirochæte.—The parasite occurs in the blood during the febrile stage of the disease only, often disappearing some forty-eight hours before the crisis and being very scarce or entirely absent during the non-febrile intervals. In some forms and cases it is present in large numbers in every field of the microscope; in others it is so scanty that many fields have to be examined before a single specimen can be discovered. In thin films of fresh blood it can usually be recognized by the agitation its movements communicate to the adjacent corpuscles (Fig. 34). In dried and fixed films the stains in general use for malaria work suffice.

In children, especially, the spirochætes may often be found sparsely in the blood-stream during the apyretic periods.

Dark-ground illumination is admirably adapted for demonstrating the living parasites; a very strong illuminant, preferably a high-power electric-light—not always procurable in the tropics—is required. Occasionally, when very scarce in the blood-stream, as during a relapse, or in the clinical form met in North Africa, the organism may best be demonstrated by the "thick-film" method. Chung in China has demonstrated these spirochætes in the urine, but this appears to be quite exceptional.

Cultivation.—The successful cultivation of *S. recurrentis* and its sub-varieties was first obtained by Noguchi and others in sterile ascitic fluid containing citrated blood and a small amount of fresh kidney, incubated at 37° C. The greatest multiplication of the organisms takes place at the junction of the ascitic fluid and of the blood. Anaërobiosis is necessary and also the presence of coagulated albumin. The *p*H value is of great importance. The spirochætes reach their maximum development on the seventh to the ninth day, after which they begin to disintegrate. Subcultures retain their virulence for mice.

Chen in Peking obtained cultures on chick embryo. Blood containing *S. recurrentis* was inoculated beneath the chorio-allantoic membrane. A good growth of spirochætes was seen in the blood of the embryo reaching its maximum on the fifth day.

Meleney found that the grey squirrel (*Sciurotamias davidianus*) and the striped chipmunk (*Tamias asiaticus*) can be experimentally infected with the Chinese strain. After splenectomy the virulence of the attacks in these animals was increased.

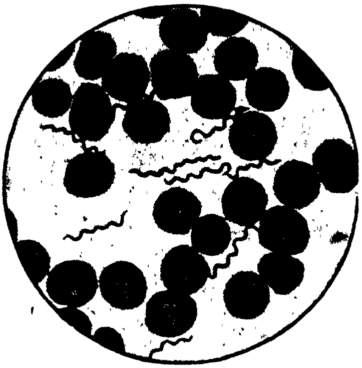


Fig. 34.—*Spirochæta recurrentis* in blood-film. × 500. (*Microphotograph: Dr. John Bell.*)

Different strains of relapsing-fever parasites (*see* Table II, p. 187).—In one part of the world the human spirochæte is transmitted by one species of blood-sucking arthropod, and in another part by another. The serum reactions of these parasites differ, and the fevers they cause are, in some respects, clinically different. The parasite, as originally described in Europe, is known as *S. recurrentis*. The Persian form of the disease (mianeh fever) was thought to be clinically distinct, and due to *S. persica*, the Central African disease, popularly known as tick fever (or carapata disease), being due to *S. duttoni*. The South American form is known as *S. venezuelensis*. In 1926 de Buen described a new variety, more resembling the Central African form, which is transmitted by ticks (*Ornithodorus marocanus* and *O. erraticus*) which live in the burrows of rats and porcupines, and the parasite has been named *S. hispanica*. In Turkmenistan a strain (*S. persica* or *S. sogdianum*) has more recently been found to be transmitted by *O. papillipes*, which has proved to be the carrier there and also in Palestine, Persia and N.W. India.

Clark and Graham originally suggested that a tick-borne infection might occur in the Colarado Valley, Texas, and in California. Now it has been described by Wheeler, Herms and Meyer as due to *S. turicatæ*. It is transmitted by *Ornithodorus hermsi*, *O. turicata*, and possibly by *O. parkeri* (*see* Appendix, p. 948).

White mice and white rats are especially susceptible to these spirochætes, the former particularly so, the organisms appearing in the blood within twenty-four hours of inoculation and persisting to the third day. About this time they disappear for several days from the blood until the commencement of the first relapse, which may be followed by a second, third, or even a fourth, the number varying in individual mice; with each relapse the parasites reappear in the blood. The interval between the relapses is generally about seven days; occasionally it is only two, though it may be as many as ten. The actual number of organisms in the blood in the first is greater than in subsequent relapses, indicating the development of a partial immunity. Recovery in mice is the rule.

As a result of the consecutive passage of the spirochæte through a long series of rats, its virulence is augmented, so that the incubation period becomes reduced to 15–18 hours, and the persistence of the parasite in the blood is prolonged to 60 hours instead of, as originally, 48 hours; at the same time the spirochætes become far more abundant.

Emerson, Mossman, Beunders, Rothermundt and others showed that some spirochætes have a definite neurotropic tendency, and that after subinoculation of *S. duttoni* in mice a residual brain infection persists.

In rats an acquired immunity may be produced which lasts for many months. As a rule, *S. duttoni* produces a far more severe disease in these animals than does *S. recurrentis*.

Rabbits and guinea-pigs are relatively refractory.

Dogs, rats and guinea-pigs are refractory to *S. venezuelensis*. Man and certain squirrel monkeys seem to be the chief reservoir of the virus. Mice which have been made immune to *S. duttoni* can subsequently be infected by *S. venezuelensis*.

Pathology.—The spleen is usually large and soft, often shows multiple infarcts and fibrinous exudates, and may rupture spontaneously. Perisplenitis is common. Sections of the spleen and liver show spirochætes within the endothelial cells. They are very abundant in necrotic lesions in the Malpighian bodies. These constitute an important basis in the differential diagnosis from yellow fever, with which virulent cases may be confused. Liver, kidneys, and heart show cloudy swelling of their cellular elements. The skin in fatal cases is usually jaundiced, and there may be subcutaneous petechiæ. The bone-marrow is hyperæmic, and shows great activity of the leucoblastic elements. There is generally a marked polymorphonuclear leucocytosis. Spirochætes are often phagocytosed by the leucocytes, but disappear rapidly after death. During the apyrexial periods an occasional spirochæte may be found in the peripheral blood by injecting intraperitoneally not less than 25 c.c. into a susceptible animal, which must be examined twice daily for the succeeding ten days before a negative result can be claimed.

In Germany and Austria strains of relapsing fever spirochætes have been used for therapeutic inoculation in the same way as malaria. As the result of this study, it has been established that the spirochætes may be demonstrated in the liver, brain and cerebro-spinal fluid and that active infection may be produced by inoculation of susceptible animals with material obtained during the quiescent periods and even after apparent recovery.

Sagel showed that infection produced by the bite of a tick is much more virulent than that brought about by direct inoculation. Pampana considered that the relapsing-fever spirochætes are remarkably neurotropic, and in guinea-pigs the brain and cerebellum are still infective fourteen months after primary inoculation. A great deal of attention has recently been paid to fixation in the brain of mice and birds. Similarly, Mathis and Durieux showed that strains

TABLE II
SYNOPTICAL TABLE OF VARIOUS FORMS OF *SPIROCHÆTA* AND CLINICAL SYMPTOMS OF THE RELAPSING FEVERS THEY EVOKE IN MAN

Habitat and Strain.	COSMOPOLITAN: N. AND S. AMERICA. N. AND W. AFRICA. N. CHINA. EUROPE. INDIA. *Spirochæta recurrentis* (*obermeieri*, *novyi*).	TURKMENISTAN, PALESTINE, PERSIA and NORTH-WEST INDIA. *Spirochæta persica* (*sogdianum*).	SOUTH SPAIN AND MOROCCO. *Spirochæta hispanica.*	CENTRAL AFRICA. *Spirochæta duttoni.*	CALIFORNIA, TEXAS, IDAHO AND COLORADO. *Spirochæta turicata.*	CENTRAL (PANAMA) AND S. AMERICA (COLOMBIA AND VENEZUELA). *Spirochæta venezuelensis* (*neotropicalis*).
Animals susceptible.	Small rodents, only after passage through monkeys.	Monkeys (*Macaca*, *Cercopithecus*) rats, mice, field mice, guinea-pigs, hamsters, dogs, rabbits, badgers.	Guinea-pigs, desert foxes, jackals, and Moroccan hedgehogs, rats, mice and shrews.	Small rodents and many animals susceptible.	Chipmunks (*Tamias Sp*). Armadilloes. Squirrels (*Sciurus douglasii*)	Rats and S. American monkeys, marmosets (*Œdipomidas geoffroyi*), opossums (*Didelphis marsupialis*), armadilloes (*Dasypus novemcinctus*).
Course in animals.	Mild.	Severe.	Severe.	Very severe.	Fairly severe.	Severe.
Subinoculations in animals.	Monkey to monkey, mouse to mouse. Persisting brain lesions.	Monkey to dog, rabbit and guinea-pig.	Guinea-pig to guinea-pig.	Monkey to monkey. Positive. Shrew-mice (*Crocidura*) in Dakar. Brain infections.	White mouse to mouse and squirrel.	Rat to rat. Slightly pathogenic.
Course in man.	2–4 relapses. Incubation period 2–10 days. Duration of attack 5–6. Apyrexia 7–10.	Fairly severe attack, usually short, average 2–6 days. Relapses 1–14.	Apparently resembles the Central African form. Fairly severe with 1–6 relapses of 3–4 days each.	Severe: 5–11 relapses. Incubation period 7–10 days. Duration of first attack 3. Apyrexia 1–8 Complications severe.	Resembles cosmopolitan form.	Resembles Central African form. Many cases benign.
Natural transmitters.	Lice (*Pediculus humanus*).	Ticks (*Ornithodorus papillipes* (*tholozani*), *O. lahorensis*)	Ticks (*Ornithodorus erraticus* or *O. marocanus*).	Ticks (*Ornithodorus moubata*, *O. erraticus*). Hereditary transmission.	Ticks (*Ornithodorus hermsi*. *O. turicata* Texas). ? *O parkeri*.	Ticks (*Ornithodorus venezuelense*, *O. turicata*, *O. talajé*).
Serum reactions.	Immune serum not agglutinating *S. duttoni*.	Large numbers of strains without cross-immunity.	Immune serum not agglutinating *S. recurrentis*.	Immune serum not agglutinating *S. recurrentis*.		Immune serum not agglutinating *S. duttoni*.

N.B.—In all tick-borne infections transmission is hereditary; this does not occur in the louse-borne disease.

of *S. duttoni*, originally isolated from shrew mice in Dakar, may persist in the brains of subinoculated mice up to 235 days.

Transmission.—There are two main forms of intermediary host which transmit relapsing fever, namely lice and ticks. A reservoir of infection of relapsing-fever spirochætes may exist, especially in Africa, in the smaller rodents which appear to be naturally infected. Nicolle and Anderson in Tunis suggested that the spirochæte of these mammals, *S. normandi*, is probably identical with *S. duttoni*. This organism is virulent to rats and mice, but not pathogenic to guinea-pigs. The *hispanica* strain is equally virulent to mice, rats and guinea-pigs.

Russell in Accra (Gold Coast) found the pouched rat (*Cricetomys gambianus*) to be most susceptible to infection with *S. duttoni*, and it is probable that the spirochæte of the shrew mouse, *S. crociduræ*, is identical with *S. duttoni*. In Panama, Clark and Dunn found a wild squirrel monkey —*Œdipomidas geoffroyi*—naturally infected with *S. venezuelensis*.

Epidemiology and endemiology.—The fever caused by *S. recurrentis* occurs, as a rule, at definite seasons of the year, depending upon the circumstances which favour the propagation of the intermediary host, the body-louse. In times of peace the poorer and indigenous class of the community is attacked. In Europe, for instance, relapsing fever has been a feature of famine, as has long been noted in Ireland, where it was once known as " famine fever." Widespread epidemics have occurred among the partially starved population of Central Russia. In war-time it is the scourge of armies in the field, and is commonly associated with epidemics of typhus, itself also a louse-borne disease ; therefore the two infections may co-exist, as in the great Serbian epidemic of 1915. In Southern Europe and Northern Africa relapsing fever is a disease of the winter and spring months, at which time people are wont to envelop themselves in thicker clothes than usual and to congregate together for warmth, thus facilitating transmission. Alarm was caused by the rapidly advancing and widespread epidemics of louse-borne relapsing fever which swept across Africa in 1921, starting from Upper Guinea. In two years the number of deaths caused in the French Sudan and the Niger was estimated at 80,000–100,000. In the upper Volta area it caused 20,000 deaths, and in 1926 in Darfur it killed over 10,000 people. Generally speaking the louse-borne disease is uncommon in Equatorial Africa, on account of the scantier clothing. In Dakar and certain parts of Senegal, however, the infection is tick-borne, and the spirochæte is said to be identical with *S. duttoni*. In India it has been noted that at the advent of the hot weather, in April and May, the lice die off and the epidemics of relapsing fever come abruptly to an end.

The epidemiology of tick-borne relapsing fever differs from that of the louse-borne disease, as the former is associated with houses and localities which form a suitable environment for *Ornithodorus*, and is transmitted hereditarily. In Central Africa it has been known for many years that the " rest-houses " on the main routes of travel are endemic centres of this fever, for the ticks live in the mud walls and roofs of the huts, and emerge at night-time to feed on man. There is therefore no seasonal incidence, as in louse-borne relapsing fever. The same has been noted in the South

American tick-borne form, except that a greater incidence is observed in the wet and rainy season, when native labourers and oil prospectors are necessarily more confined to their quarters.

Evolution of the parasite in the intermediary host.—Philip Ross, Milne, Dutton and Todd showed definitely that *S. duttoni* is normally conveyed by *O. moubata*, and that it can be transmitted, not only by the tick which has bitten the infected individual, but also by its progeny, even to the third generation (Koch). The spirochæte has even been demonstrated within the eggs laid by infected ticks. From these eggs nymphs are produced in which the organism multiplies. Once fed on spirochæte-containing blood, ticks remain infective for one and a half years, and can convey relapsing fever by successive bites to at least ten monkeys (Plate VI facing p. 226).

Wheeler, Herms and Meyer found a new tick vector in California in *Ornithodorus hermsi*, which they collected from Lake Tahoe, Big Bear Lake, San Bernardino, Eldorado and Placer counties, at an elevation of 5,000–8,000 feet. These ticks were found naturally infected with the Californian strain, and produced infection in mice and monkeys. Chip-munks and squirrels, which abound there, seem to be the reservoirs of infection. The bites of both male and female ticks in all instars are infective.

Development in the tick.—The cycle of development differs from that in the louse in that some spirochætes enter the solid organs of the tick, the cells of the gut, the Malpighian tubules, and the coxal and salivary glands. Some can even be found in the ovaries. They remain motile for several days after ingestion into the stomach, the duration depending on temperature. Complete development usually takes about ten days, after which time the spirochætes congregate in large numbers in the hind-gut, when they are ready to infect man.

Transmission is effected by the saliva, excrement and secretion from the coxal glands. When the tick feeds again on blood it makes a relatively large puncture in the skin and the saliva is delivered at the base of the mouth parts, so that presumably none enters the wound, but towards the end of feeding the tick evacuates the contents of its hind-gut, consisting partly of fæces and partly of nitrogenous waste from the Malpighian tubes. Fluid is also excreted from the coxal glands through an aperture at the base of the front legs. In *O. moubata* this occurs while the tick is still feeding. (Fig. 321).

Transmission has been proved to be direct by bite from *O. papillipes* (Adler) and *O. hermsi*, as these ticks do not pass fæces or coxal fluid when biting. If the puncture wound in an experimental animal be scraped and smears made, spirochætes can readily be demonstrated. Relapsing fever spirochætes may survive within ticks for as long as 6½ years.

Development in the louse.—According to Nicolle *S. duttoni* cannot be transmitted by lice. The louse absorbs 1 mgm. of blood, which may contain large numbers of spirochætes[1]. One day after ingestion they may be discovered in the insect's midgut (at 28° C., 82° F.). At this stage some spirochætes attach themselves to the epithelial cells lining the others invade the cells, while many die in the gut. By the end

---

recurrentis.

of the first day the spirochætes have disappeared, and there then follows a phase during which they can seldom be found in any part of the body. This was thought to be a "granular" phase, as in the tick, but this question has been difficult to decide as the tissues contain so many minute granules. Adler and others now reject this possibility and consider that the organisms persist as spirochætes, though difficult to find. After the eighth day (or even after a few hours—Chung and Feng, 1936) spirochætes appear in the blood of the louse, circulating through its body cavity. They then increase rapidly and may be found in all parts of the body and limbs, but not in the lumen of the gut or inside the salivary glands and ducts.

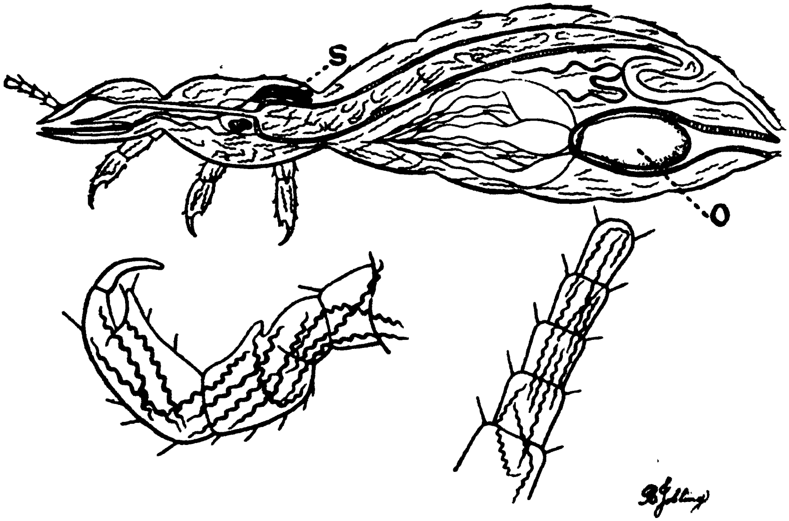


Fig. 35.—*Spirochæta recurrentis* **of relapsing fever and its development in the louse** (*Pediculus humanus*). (*C. M. Wenyon, Trans. Roy. Inst. of Great Brit.*)
Diagram shows whole body invaded by spirochætes. S, salivary glands; O, egg. Below, spirochætes in leg and antennæ, which are easily broken off, so that fluid exuding from the body infects the skin of the host.

These fully developed or metacyclic spirochætes persist in the body of the louse throughout its life, without detriment. Thus, a considerable proportion of lice taken from a relapsing fever patient may be found infested (Fig. 35).

When the spirochætes have reached the body cavity of the louse they have no natural means of egress and the louse can then bite man with impunity, but if a leg or antenna is injured or broken, the spirochætes escape and will enter any scratch or abrasion. Transmission probably normally takes place by man rupturing the louse and inoculating himself while scratching. As crushing kills the insect, one louse is capable merely of causing relapsing fever in one individual and, therefore, for this disease to assume epidemic form lice must be very abundant.

Under optimum conditions 48 per cent. of lice become infected and remain so for 28 days. It is very unlikely that any spirochætes escape in the louse excreta. There is no evidence of hereditary transmission in this insect. (The crab louse, *Phthirus pubis*, appears incapable of transmitting the spirochæte.)

Bed bugs.—Transmission by the bed bug, *Cimex lectularius*, has been suggested often since the time of Tictin (1897), but no convincing case has been made out for it under natural conditions.

Other methods of transmission.—The spirochætes have been proved capable of penetrating the mucous membrane and, if well rubbed in, the unbroken skin. Nurses and doctors treating relapsing-fever patients have been inoculated through the entry of infected blood into the conjunctival sac, and in pregnant women and experimental animals it has been proved that the organism can pass through the placenta to the fœtus. A particularly virulent infection is commonly found in China in heroin addicts, conveyed by dirty syringes, like subtertian malaria (*see* p. 49).

Immunity.—Sabritschewsky, in 1896, showed that, when equal parts of spirochæte-infected blood or serum and normal serum are mixed, the spirochætes survive longer than when the infected blood is mixed with that of a patient who has recovered from relapsing fever. He accordingly concluded that the cause of the crisis in relapsing fever and of subsequent immunity was the development of a germicidal substance in the blood. He was the first to apply serum-therapy, and obtained an anti-spirochæte serum by repeated innoculation of the horse with human spirochæte-containing blood.

Treated *in vitro* with hyper-immune serum, the spirochætes rapidly become unrecognizable aggregations of granules, and this phenomenon may be manifest in a dilution of 1 : 2000.

Cunningham in 1925 showed that the spirochætes which are found in the blood in the initial attack differ serologically from those which bring about the first relapse, and, on inoculation into animals, these strains maintain the same characteristics. Thus, if strain A be inoculated into an experimental squirrel, the initial attack will be of that serological strain, but in the subsequent relapse the strain will be B; but if the B strain be inoculated, the relapse will be A, and so on. There is thus an alternation of serological strains. It is probable that the antibodies produced in the blood-stream by one particular strain do not persist long enough to prevent relapse. The thrombocytobarin (Rieckenberg) or adhesion phenomenon shows clearly that serological differences exist between the spirochætes of the first attack and those of the second.

General Symptoms Common to all Forms

1. Epidemic cosmopolitan louse-borne type (*Spirochæta recurrentis*).—The course and character of the disease vary greatly in a single epidemic, and, further, the virulence of the more severe forms is much greater in some outbreaks than in others. The *incubation period* usually lasts from two to ten days. In some instances the attack develops promptly on exposure; it is never delayed beyond the fourteenth day. In the artificially inoculated, symptoms show themselves in from two to six days.

The *onset* is generally abrupt, being characterized by chilliness or rigor, giddiness, epistaxis[1], vomiting, photophobia, intense headache, and pain in calves. In the young there may be convulsions. Temperature rises rapidly to 104° or 105° F., sometimes to 108° (Chart 8). The pulse is rapid, 110 to 130. Should fever run high, there may be delirium. The skin is dry, although, especially during the first day, occasional sweats may break out. A slight icteric tinting of the conjunctiva is usual and,

[1] This has been a prominent sign during this war, especially in Abyssinia.

not infrequently, jaundice is marked at the crisis. The spleen is invariably enlarged and tender. The tongue is coated and moist, except in bad cases, when it may become dry, brown, and painful on protrusion. The bowels, as a rule, are confined; abdominal pain may be considerable, and patients usually complain of pains in the muscles of the legs, especially the calves. Occasionally, herpes labialis is noted. There is quite commonly an erythematous rash in the initial fever, and later, rose-coloured spots on the trunk and limbs; some authors describe petechiæ. The rash has a peculiar distribution, being generally most marked round the neck, spreading in a semicircular fashion from the tips of the mastoid processes; thence it ranges symmetrically round the shoulders, down the sides of the chest and abdomen to the inner aspect of the thighs, and to the extensor and flexor aspects of the forearms. The individual petechiæ may be as large as a threepenny bit, and need to be carefully differentiated from the exanthemata of typhus and hæmorrhagic smallpox. They are not easily seen on a dark skin.

The primary remittent fever may last from five to seven days. At first the morning is usually lower than the evening temperature, but on or about the third day the evening temperature rarely rises above that of the morning. On the fourth, fifth, or sixth day there is again a rise of temperature, sometimes with delirium, ending in a crisis of profuse sweating and diarrhœa. The temperature now falls rapidly to normal or subnormal, sometimes dropping in a few hours as much as 12° F.; in elderly or delicate patients there may be dangerous collapse.

The initial pyrexia, called *first paroxysm*, is followed by a *first period of apyrexia* during which the patient recovers so rapidly that after four or five days it may be difficult to keep him in hospital. But from seven to nine days after the crisis, that is about the fourteenth from the commencement of the attack, rigor again occurs, followed by a second attack of fever—*first relapse*. This may be more severe than the initial paroxysm; usually it is milder, and seldom lasts so long. During it the secretion of urine is considerably increased; sweating also is profuse, and prostration marked. A polymorphonuclear leucocytosis of 15,000 to 30,000 is found during the pyrexial periods.

With the defervescence of the first relapse the patient enters on the *second period of apyrexia*, which is usually coincident with convalescence (Chart 8). But in some patients a *second relapse* may occur, usually about the twenty-first day, counting from the onset of symptoms. This second relapse rarely lasts longer than three days, and is generally milder than the previous paroxysms. In rare instances three, four, five or even more relapses have been observed. Anomalous types of fever are common. Some temperature charts show an intermittent fever throughout, more resembling that of phthisis. Cases with four relapses in a period of twenty-six days are met. Occasionally the apyrexial period may be of considerable length—seventeen days; in one case observed, forty-two days. In some epidemics chronic diarrhœa, in others arthritis, is a feature.

Convalescence may be protracted, and complicated with such sequelæ as nephritis, ophthalmia, iritis, œdema of the eyelids, otorrhœa, polyarthritis, pneumonia, neuritis, parotitis, and adenitis. A mild type of encephalitis has been noted in the present war (1943). In pregnant women abortion is the rule. In some cases attacks of abdominal pain resemble appendicitis.

Bilious typhoid form.—This is thought by some to be a distinct disease and on account of the severity of its symptoms and rapidity of its course, especially on the West Coast of Africa, is apt to be mistaken for yellow fever. High fever, epistaxis, dyspnœa, intense jaundice, and enlargement of the spleen are noted. The jaundice is probably due to toxic hepatitis. The liver is enlarged. The purpuric rash is a thrombocytopenic purpura and is associated with hæmorrhages from the mucous membranes. Hæmorrhages into the skin and from the internal organs commonly occur; marked albuminuria is the rule.

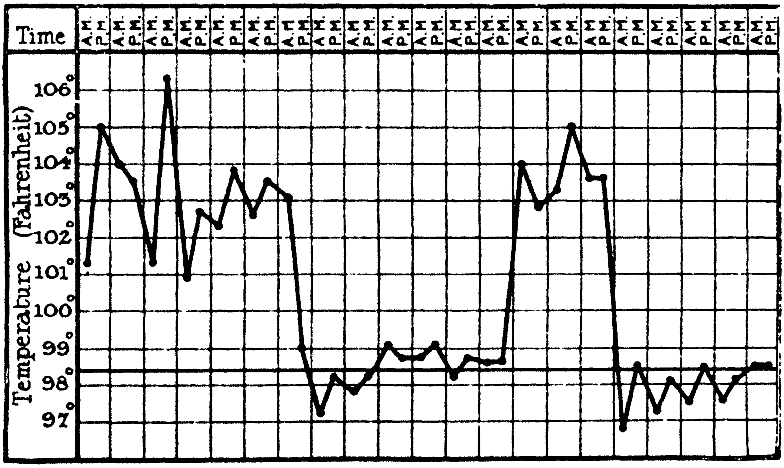


Chart 8.—Relapsing fever, cosmopolitan louse-borne type.

Some cases become stuporose, with tympanites, hiccough, and severe diarrhœa. In Abyssinia intense dyspnœa was a prominent feature. These severe forms are more generally seen in war-time, when with starvation and exhaustion, the disease assumes a more serious aspect.

II. Persian type (mianeh disease).—This tickborne type is due to *Spirochæta persica*. It is found throughout Persia, and apparently also in Syria, Libya and Palestine. The symptoms may be said to be intermediate between those of the epidemic louse-borne and those of the Central African type, for, as compared with the former, the relapses are more numerous and of shorter duration, while the organisms are very scanty in the peripheral blood, requiring a thick-drop method for their demonstration (Chart 9). The attack is generally moderately severe; the initial pyrexia shows marked morning intermissions, and lasts four to five days, when the temperature comes down either by lysis or by crisis. Three, four, five or even more relapses are often noted, lasting sometimes only twenty-four hours, or, at a maximum, three days. The spleen is

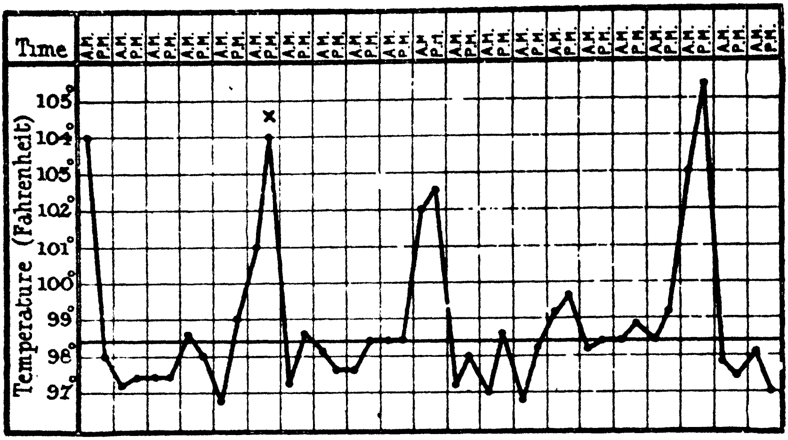


Chart 9.—Relapsing fever, Persian type. (*Bellingham Smith.*)
X Spirochætes demonstrated in blood-film.

rarely enlarged, and icterus does not usually occur, but, according to Harold, in certain epidemics the disease may assume a more severe aspect, jaundice and other complications may supervene, and the mortality may be high.

III. Central African type (carapata disease; tick fever; gorgoya, Somaliland) (*Spirochæta duttoni*).—The African tick-conveyed relapsing fever, caused by *S. duttoni*, although in type of fever resembling the classical epidemic European and Indian forms, differs in some important particulars. The initial fever is not usually so prolonged, generally terminating by crisis within three days. Diarrhœa and dysenteric symptoms are not uncommon. The apyretic intervals are of very irregular duration, being, according to Philip Ross, sometimes as short as one day, sometimes as long as three weeks; and instead of only one or two relapses, as in ordinary relapsing fever, there may be as many as eleven, five or six relapses being the rule (Chart 10). The fever, though shorter, is as severe in the relapses

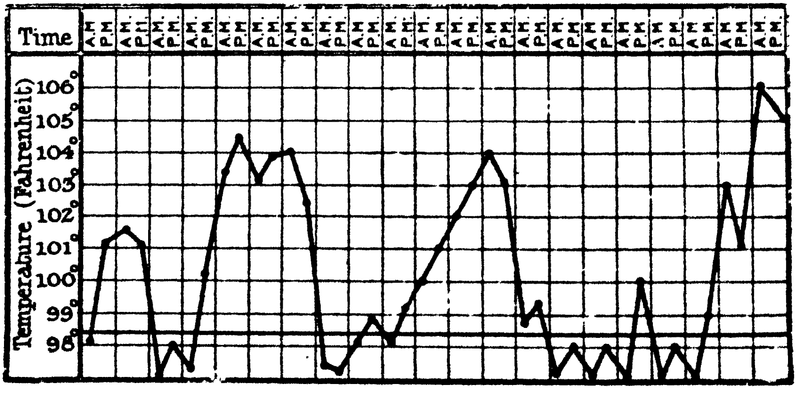


Chart 10.—Relapsing fever, Central African type. (*Newham.*)

as in the initial paroxysm, but the intervals tend to become longer, though there are exceptions. Sometimes the fever may assume a low chronic form, perhaps a sharp cutting pain in the nape of the neck, and vomiting. Iritis or iridocyclitis, uni- or bilateral, is a not uncommon complication or sequela. The liver and spleen are generally enlarged, and jaundice, bronchitis and pneumonia are frequent complications. The parasites, being usually very scanty in peripheral blood, may be hard to find. There is a polymorphonuclear leucocytosis, as in the louse-borne type, and a slight aplastic anæmia.

Fulminating cases, in which the onset is very sudden, were observed nine times in a study of 1,500 cases during the East African campaign (1914–1918) by J. K. Manson and Thornton. In these the spirochætes occur in enormous numbers; coma and death may ensue within twenty-four hours. Sometimes there is most intense icterus. These observers considered that death is brought about by impaction of masses of spirochætes in the cerebral capillaries.

In natives of the endemic districts the disease, as generally observed, is not nearly so severe as in Europeans and strangers, being usually limited to a paroxysm or two of one or two days' duration. The mildness of these attacks is probably explained by a partial immunity conferred by previous infections.

Implication of the central nervous system, due to invasion by spirochætes, is not uncommon. A particularly distressing, but fortunately somewhat rare, complication is optic atrophy. Of this there are two forms —one which follows immediately upon the cessation of the fever, the other which gradually develops after the lapse of several months. Some observers have described aphasia, facial paralysis, hemiplegia, and implication of the cranial nerves—such as the third, fourth, and sixth (resulting in ptosis and strabismus), the fifth (trigeminal neuralgia), the seventh (facial paralysis), and the eighth (deafness)—coming on suddenly during the course of the disease; some have recorded signs of meningitis. In these nervous complications spirochætes may sometimes be demonstrated in the cerebro-spinal fluid; as a rule, it contains an excess of lymphocytes and is under considerable pressure, necessitating lumbar puncture in order to relieve symptoms. Hawking in Tanganyika failed to find spirochætes on microscopic examination of cerebro-spinal fluid, but intraperitoneal injection into mice produced infection. In patients infected with subtertian malaria a superimposed attack of this relapsing fever may determine the onset of blackwater fever. Arthritis is not uncommon.

IV. Tick-borne Spanish type (*Spirochæta hispanica*).—The most complete study of the clinical aspects of this form of relapsing fever is by Más de Ayala (1931). The incubation period is apparently very short, 1–2 days, and the onset of the fever is abrupt. It is ushered in by nausea, headache, chilliness, general malaise, a rise of temperature to 40° C. (104° F.) with congestion of the face and eyes, and dryness of the mouth and lips.

The *initial pyrexia* persists for 3–4 days and is associated with drowsiness and prostration, and generally with enlargement of the spleen. There is the usual rapid fall of temperature at the crisis, often associated with collapse, which responds to injections of adrenalin.

The periods of apyrexia and relapse correspond closely to those of the Central African form. After four attacks the disease apparently comes to an end spontaneously. The Spanish form of relapsing fever does not seem to be associated with secondary anæmia, as in the other forms, though there is generally a leucocytosis of 14,000 to 26,000 per c.mm. during the attacks. Herpes labialis is common, and the urine often contains bile at the crisis. Enlargement of the cervical lymphatic glands said to occur.

As in *S. duttoni* infections, nerve complications have been noted. Facial paralysis has been seen in about 3 per cent. some six weeks after the last relapse, and in about the same proportion of cases iritis is noted.[1]

The prognosis is usually good. The immunity to this strain of spirochæte appears to last about a year.

V. TICK-BORNE, CALIFORNIAN, CENTRAL AND SOUTH AMERICAN TYPES (*Spirochæta turicata* and *S. venezuelensis*) present no special clinical features, but resemble in the main Central African tick-fever.

Ocular complications of relapsing fever.—These were studied by Hamilton (1943) in the Middle East. They are thought to be due to the presence of numerous spirochætes in the ocular blood vessels. Acute iridocyclitis merges into chronic cyclitis with persistent headache. Posterior synechiæ develop, and may be broken down by midriatics. A gross vitreous exudate is marked. Despite cyclitis and vitreous changes, no choroiditis is observed. Prognosis for vision is good. These complications are specially marked in the louse-borne type.

Mortality of relapsing fever.—The death-rate is usually below 6 per cent. In a serious form with jaundice, which has been noticed on the West Coast of Africa, the death-rate may exceed 50 per cent. In the feeble and old, death may ensue at the height of the first paroxysm, or from exhaustion as the result of relapses.

Diagnosis.—This fever is most usually confused with subtertian malaria, from which it may be undistinguishable on clinical grounds ; it may also resemble leptospirosis, enteric, typhus, influenza, dengue, pneumonia, malignant smallpox, and even plague. In South America and West Africa it may be confused with yellow fever. The detection of the spirochætes with the microscope, or by animal inoculation, is the most reliable method of diagnosis, especially during the febrile paroxysms. They are readily demonstrated with the dark-ground illumination. For methods of staining, *see* p. 1013. At an early stage the relapsing character of the fever is not available as an aid to diagnosis, but at a later period the history of a fever which had relapsed about fourteen days from the onset of the disease should be regarded as highly suggestive.

Wassermann reaction.—A strong pseudo-positive complement-deviation is obtainable, both during the pyrexial stage and in the apyretic periods between the early relapses, in about 20 per cent. of cases. This apparently applies to all clinical types of the disease and therefore does not necessarily indicate a syphilitic infection.

---

[1] In the campaigns in the Libyan Desert Scott reported nerve-complications in 22 per cent. This spirochæte is neurotropic, so that meningitis, hemiparesis, facial palsy and ophthalmoplegia were noted. The *c.s.f.* is under pressure with lymphocytic pleocytosis and increased protein and globulin : rarely spirochætes were present.

Treatment.—Careful nursing and dieting are necessary, especially in the African type, and must be maintained after the crisis, when the patient is ravenously hungry.

(1) *Salvarsan.*—Salvarsan and its allied preparations are specific when injected intravenously in doses of 0·3 grm. to 0·9 grm., according to the age of the patient and the severity of the case, the dosage being reckoned as 0·01 grm. for each kilogram of body-weight. After a short aggravation of symptoms a crisis takes place with disappearance of spirochætes from the blood and, in the vast majority of cases, recovery. Should relapse occur, a second injection may be given. Of the salvarsan (arsphenamine) compounds, undoubtedly novarsenobillon is the best ; neosalvarsan, luargol, arsalyl, kharsivan, galyl (0·35 grm.) and salvarsan are useful in a descending order of merit, and recently sulphoxyl-salvarsan (Höchst) has given good results. The last mentioned, as also sulphostab (Boots), in doses ranging from 0·3 to 0·6 grm., has the additional advantage that it may be given by the intramuscular or deep subcutaneous routes. Evidence shows that salvarsan is most efficacious when given in the pre-critical period—that is, when the temperature is on the rise, directly the diagnosis has been made ; relapses are apt to occur if it is given while the temperature is *on the fall*, or during the apyretic period ; this is especially true of the Central African type, some cases of which appear to be resistant to salvarsan treatment. If it is not given in the first attack, it should be withheld until the first relapse, and then injected on the rise of temperature. It is generally agreed that salvarsan ought not to be injected when the crisis is imminent. A very grave reaction, due to the great destruction of the spirochætes and the liberation of their toxins, with corresponding aggravation of the symptoms and, it may be, fatal collapse, is apt to ensue. On the other hand, the great majority of otherwise healthy patients recover from most forms of relapsing fever without any specific treatment, although convalescence may be prolonged. Albuminuria does not constitute a contra-indication to salvarsan treatment.

Hawking, who made a study of various methods, found the results of arsenical treatment difficult to evaluate. *Arsant*, a salvarsan compound, in which one or two arsenic atoms is replaced by antimony, has the same therapeutic value as neosalvarsan. The results of treatment of the tick-borne relapsing fever in Libya (1942), especially in Tobruk, with intravenous arsenicals, were not satisfactory. Cooper reported that relapses occurred in 40 out of 57 cases.

Apparently, arsenic-resistance is rapidly acquired by these spirochætes, so that Moretti and others who studied this problem found that arsenical compounds, which are efficacious in the earlier stages of relapsing fever, may be ineffectual if a prolonged period (say of 100 days) is allowed to elapse between the experimental infection with the spirochæte and the administration of the drug.

(2) *Stovarsol, or spirocid* (van Hoof).—Stovarsol tablets (4 gr.) in doses of six daily are said to be efficacious in relapsing fever, when, for any reason, intravenous injections cannot be given.

(3) *Other compounds.*—It was claimed in Tanganyika that in *S. duttoni* infections intravenous injections (20 c.c. of a 1 per cent. solution) of mercurochrome are beneficial. Gold compounds were advocated by German workers—Solganal B and A.69 ; the former contains 36·5 per cent. of gold. It is claimed

that residual infections in the central nervous system are eliminated. Both preparations may be given intravenously or intramuscularly. Ishii and his colleagues carried out investigations with various sulphonamide preparations without positive results.

(4) *Subsidiary methods.*—The collapse and fall of blood-pressure with subnormal temperature which follow the crisis have to be counteracted by strychnine, brandy, intrarectal douches of hot salines, and by injections of adrenalin and ephedrine. Vitamin K is indicated for the hæmorrhages.

Prophylaxis (*see* Table III).—In the louse-conveyed forms of relapsing fever prophylactic measures are necessarily aimed at the destruction of lice and their eggs by all the measures known to sanitary science—often a matter of very considerable difficulty when dealing with large groups of native porters or labourers, especially during the rainy season. Disinfestation is performed by superheated steam in a portable Thresh's disinfector, or in specially constructed cars in a disinfecting train, the superheated steam being supplied by the locomotive. As head lice can convey relapsing fever, local measures, such as application of *oil of sassafras* to the head, must be undertaken. (For recent measures of louse destruction, *see* p. 233 and also Appendix, p. 991).

In the African form, prophylactic measures are much more difficult, and necessitate an intimate knowledge of the habits of ornithodorus, which does not live on the body of its victim, but emerges at night-time from the native houses to feed on blood. It is also found on the veld, living in the burrows of the wart-hog, but as a rule it is only met in numbers in the vicinity of old camping sites (*see* p. 946). The tick itself is very difficult to destroy, and may remain uninjured after prolonged soaking in cresol.

The following rules are necessary :

1. Avoidance of native houses, most of all at night-time—especially those situated on much-frequented routes. Bedsteads of native manufacture should also be avoided. Camps should be placed as far distant as possible from native villages.
2. Avoidance of much-frequented ground for camping sites ; ornithodorus can exist without food for years. Sleeping on the ground should not be practised unless absolutely necessary, and only when well protected by a mosquito-net. A night-light is recommended to scare away the ticks. Blankets should be carefully inspected before retiring to rest.

Native huts should be so constructed that a space of 8–10 in. intervenes between the walls and the ground. Mud and rubble buildings are inadvisable ; floors should be raised, and made of cement. A deep trench dug round a building and filled with wood-ash has been found effective in excluding ticks. A solution of pyrethrum in white oil (0·18 per cent.) has been found an efficient insecticide for *O. moubata*, applied either directly to the ticks or to floors or bedsteads.

Children especially act as a reservoir of the spirochætes, and the ticks feed upon them.

Prophylactic inoculation.—Attempts to immunize the inhabitants of an infected district have been undertaken by Russian workers with a vaccine

TABLE III

	Epidemic Louse Relapsing Fever	African Tick Fever	Other Tick Fevers
Vector ..	*Pediculus humanus.*	*Ornithodorus moubata.*	Other species of Ornithodorus
Haunts ..	Human body and clothes.	Floors, cracks, courtyards.	Rodent burrows.
Transmission	Crushed lice: not hereditary.	Coxal fluid, fæces; hereditary.	In some cases doubtful; hereditary.
Reservoirs ..	Man.	Probably man only. Maybe mice or shrews.	Rodents, squirrels and other animals.
Biology ..	Pediculus feeds only on man; short-lived.	*O. moubata* feeds mainly on man; lives for months or years.	Species of ornithodorus feed on animals; occasionally on man; live for months or years.
Disease type ..	Epidemic.	House disease.	Sporadic.
Control ..	Louse control.	Destruction of buildings. Concrete dwellings. Kerosene emulsion. Pyrethrum in oil.	Difficult; based on habits of normal hosts or ticks.

composed of a mixture of cultures of the original and relapse strains of *S. recurrentis*, which had been incubated at 37° C. for three days and subsequently kept at room temperature for 14–16 days until they had lost their virulence. Each man received 1·0, 1·5, and 2·0 c.c. at three days' interval. A week after the last injection the blood was found to contain spirochætolysins against both original and relapse strain. The results showed that it was possible to produce immunity by inoculation of dead spirochætes.

For a description of the ticks (Plate VI) and their habits, *see* p. 946.

General considerations on varieties of relapsing fever.—In the present state of our knowledge it is difficult to assess the exact status of the geographical varieties of relapsing fever spirochæte and their relative zoological rôles. It may well be that they are not distinct species, for they cannot be differentiated on morphological or cultural grounds. Leishmania and rickettsia offer parallels in this respect. It is doubtful whether differentiation of these spirochætes has proceeded far enough to prevent interchange of intermediary hosts. Though it has been stated that tick-borne relapsing fever organisms are not infective for the louse, this has been challenged by many workers, including de Buen, who has been able, with equal facility, to transmit *Spirochæta hispanica* through ticks or lice, while under natural conditions there is no evidence that the disease is transmitted by lice. The parasite has become habitually tick-transmitted. It has been suggested (Nicolle and Anderson, 1936) that relapsing fever was originally endemic and tick-transmitted, but as a result of the advent of a new host in the louse, it became epidemic and world-wide.

CHAPTER VII

LEPTOSPIROSIS

During recent years it has become possible, through the discovery that certain delicate spirochætes (leptospiræ) are present in the bloodstream and in various viscera, to group together certain fevers which have certain clinical features in common. Under the heading of Leptospirosis are included infectious jaundice, seven-day fever, and possibly other certain less well-defined types.

WEIL'S DISEASE

Synonyms. Icterus Gravis; Spirochætosis Icterohæmorrhagica; Mediterranean Yellow Fever; Griesinger's Disease; Odan-eki (Japanese).

Definition.—A fever, especially found in sewer workers, caused by *Leptospira icterohæmorrhagiæ*, associated, though not invariably, with jaundice and enlargement of the liver. The natural reservoir of infection is usually the rat (*Rattus rattus* and *R. norvegicus*).

History.—An acute febrile illness associated with jaundice and a high mortality was first described by Weil in 1886, and has since been known as Weil's disease. Possibly Larrey originally described this disease as contagious jaundice with hæmorrhages in Egypt in 1812. In 1915 Inada, Ido, and other Japanese investigators described the spirochæte *L. icterohæmorrhagiæ* as the cause of the disease, and this was confirmed in Germany by Huebener and Reiter in the same year. In the early summer of 1916 this disease occurred sporadically among the allied and German troops in France, where the Japanese discovery was soon confirmed by Stokes, Ryle, and Tytler among British troops, and by Uhlenhuth and Fromme on the German side, while Bonini recognized it on the Italian front. In 1917 the same Japanese investigators, by guinea-pig inoculations, proved the presence of the leptospira in otherwise healthy rats (*R. norvegicus* and *R. alexandrinus*) and in the field-vole (*Microtus montebelloi*).

Geographical distribution.—The disease appears to be especially prevalent in Japan; during the 1914–1918 War, outbreaks occurred among troops in Gallipoli and Salonika, and also in Egypt, where the disease had long been known. It is found along the North African coast and the shores of the Mediterranean, and is known to occur in France, Italy, Germany, Holland, the United States, Peru, Brazil, and the Argentine. It is endemic in West Africa, the Congo, French Equatorial Africa, Sudan, Abyssinia, and British Guiana. Epidemics have been described in the Andaman Islands, Dutch East Indies, and Malay States (Fletcher). The disease in the tropics is said to be specially virulent, though further researches on this point, as well as on its distribution in hot countries, are necessary. In Europe it is said to be commoner in summer-time in Holland, where Schüffner observed 451 cases in ten years; it is specially prevalent in the south and in Rotterdam. The Editor, in 1922, recorded a case in London; others have been observed in Scottish coal-mines (Buchanan), and in Aberdeen. In 1934 it was shown by Fairley that Weil's disease is by no means uncommon in the sewer workers of London, and this was soon confirmed in Liverpool and other cities. It is also not infrequent in canal workers.

Epidemiology and endemiology.—In Japan the disease has a definite seasonal incidence, occurring, as a rule, most frequently in the months of September to November. The organism is found as a harmless parasite in the kidneys of wild rats and mice, and is excreted in their urine. The disease is therefore usually endemic among farmers and miners who are exposed to wet soil and water conditions, such as prevailed in trench warfare and caused outbreaks in 1916 and 1917 in France. In the Andamans, leptospirosis was prevalent during the South-West Monsoon, and confined to adult males engaged in outdoor occupations.

In some cases water appears to be the source of infection. Epidemics have been recorded among soldiers in Italy and in Germany after bathing in certain river pools. The Editor (1922) originally showed that polluted water was responsible. Since then several other British infections from the same source have been reported. It is now known that spirochætes of the leptospira type are widely distributed in water, and some have been proved pathogenic to guinea-pigs (Zuelzer).

In Holland Schüffner showed that the highest incidence is amongst those whose occupation brings them near canals, and especially those who have fallen in by accident.

Schüffner demonstrated that the non-pathogenic *L. biflexa* (Zuelzer) occurs in any kind of water, but that pathogenic *L. icterohæmorrhagiæ* can be demonstrated by immersing experimental guinea-pigs in suspected pools.

Slime fever (*L. grippo-typhosa*) is an abortive form of Weil's disease prevalent in Germany, where it is often acquired during bathing. No less than 700 cases were reported in July, 1926. The attack begins with a rigor and a rise of temperature to 104° F. "Field fever" in pigs and man is due to *L. pomona*.

Schüffner and Uhlenhuth described outbreaks of infection with *L. grippotyphosa* in Holland and Germany, and the part played by voles (*Microtus arvalis*). Children are mainly infected during play in the fields, where they collect these rodents and are frequently bitten by them. In Switzerland the disease is known as "swine meningitis".[1]

Annual outbreaks of leptospirosis of great severity were reported in 1933 and 1934 in Queensland. These occurred among sugar-cane cutters and farmer, especially after prolonged rainfall, the infection having entered through scarifications of arms and legs; a native species of rat (*Rattus culmorum*) appeared to be the carrier of the infection. In 1934, Davidson, Campbell, Rae and Smith described an epidemic of nineteen cases in Aberdeen, chiefly among fish workers. The patients were handling fish in rat-infested premises, the floors of which became covered with slime and offal. The hands are traumatized in doing this work, so that the infection can enter. Depilated guinea-pigs were easily infected with water obtained from this source. In the United States an outbreak in fish workers was reported by Glotzer (1938). Leptospirosis has, therefore, become an "occupational disease."

The disease occurs in dogs, especially hounds, in which it is known as "the yellows," and it has been recognized in the fox, especially the silver variety, and in leopards, especially when fed on rats. Canine epidemic gastritis ("Stuttgart disease") is identical with Weil's disease.

---

[1] Since this was written it has been established that this disease is primarily a mouse infection and that there is a similar type of kidney infection to that of rats with *L. icterohæmorrhagiæ*, but in the former the leptospira is evanescent and not permanent.

Ætiology.—*L. icterohæmorrhagiæ* is found in the blood, urine, cerebrospinal fluid and sputum. It is a spiral filament with wide flexures, the individual spirals being in close apposition (Fig. 36). The largest forms attain a size of 20 μ by 0·25 μ, the average length being 6–12 μ.

It is now generally agreed that the organism is identical with *L. icteroides*, the organism described by Noguchi in yellow fever.

The organism may be demonstrated by the dark-ground illumination, but is so extremely active that its movements can only be seen with difficulty. According to Fletcher, it is most readily demonstrated in blood-films by Fontana's method. Although easily demonstrated in guinea-pigs, it can be found in human blood only after prolonged search. In microscopic sections of infected organs the leptospiræ show up well with Levaditi's method of silver-nitrate impregnation.

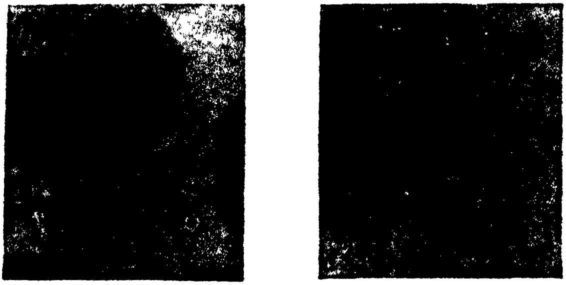


Fig. 36.—Microphotograph of *Leptospira icterohæmorrhagiæ* from kidney of rat. × 3,000. (*Dr. A. C. Coles.*)

The organisms exhibit rapid movements; when free, one end is extended and straight, the other semicircularly hooked, so that they progress in the direction of the straight portion and appear to be propelled from the rear by the rotating hook.

This parasite was cultivated by Noguchi on solid media such as blood-agar or gelatin (*see* p. 1018). According to Fletcher, it grows readily on agar impregnated with immune serum, but is agglutinated thereby in a peculiar manner. The culture medium used by Dutch workers consists of tap-water 1,500 c.c., Witte's peptone 0·15 grm., Ringer's solution 300 c.c., and Sorensen's solution of *p*H7·2. The final reaction of this peptone medium should be between *p*H 6·8 and *p*H 7·2. Three cubic centimetres is placed in a small tube and sterilized, and 3 c.c. of rabbit's serum is added. The tubes are then heated to 56° C. for thirty minutes and incubated at 37° C. overnight. Leptospiræ are seen by the dark-ground illumination on the fifth or sixth day. Stefanopoulo, Morrow and other workers have cultivated *L. icterohæmorrhagiæ* on the chorio-allantoic membrane of the chick embryo.

According to Fletcher and Brown, there are distinct serological races of *L. icterohæmorrhagiæ*, the Andaman, Indian, and Sumatran strains being distinguishable from those found in Europe and elsewhere.

Schüffner distinguished a dog strain, *L. canicola*, which occupies a position analogous to that of *L. hebdomadis* and which is found in Holland. *L. grippotyphosa* (Tarassof) is the name applied to the agent of "swamp fever," or "*maladie de la vase,*" in Eastern Europe (Korthoff); it is characterized by severe jaundice.

Fletcher and his staff in Kuala Lumpur found that the organisms isolated from 26 patients could be separated serologically into six groups, whilst Baermann and Smits in Sumatra have studied nearly 400 cases. The symptoms of this form are mild and much more closely resemble benign forms of relapsing fever. The febrile periods last from 2–4 days.

Strains of organism isolated in Queensland by Clayton and Derrick differ from those of European origin and more closely resemble Sumatran types. They were provisionally named *L. australis A* and *B* ; the latter is closely related to *L. canicola.*

There is some divergence of opinion on the advisability of regarding serological races of leptospira as distinct species. Methods of differentiation, such as the Rieckenberg reaction, are considered by some to be too delicate and uncertain.

The common natural reservoir of the leptospira appears to be the rat, in which it occurs in the fæces, urine, and kidneys, though it has not yet been demonstrated in the blood. The disease is believed to have been originally epizootic in rats, but these animals have now become tolerant. The leptospira has been demonstrated in 32·4 per cent. of wild rats in Japan, in 56 per cent. in Holland (Schüffner), less frequently in France, Tunis and Algiers, and in 4 per cent. of sewer-rats in London. In the United States the proportion varies from 4 to 33 per cent. *L. icterohæmorrhagi e* has been demonstrated by Buchanan in the zooglœa-like "roof-slime," which constitutes a source of infection in certain coal-mines in Scotland. It has also been found in the green slime of sewers in London by J. M. Alston. Probably in this case the portal of entry is through skin abrasions, and guinea-pigs have been infected by rubbing cultures, slime or suspected water through the skin. Water again may be a source of infection, especially when it comes into contact with the bronchial epithelium, as by diving and swimming the "crawl stroke" (Schüffner). In Sumatra it is thought that native dogs may constitute a reservoir, as Kowenaar and Wolf found 6 per cent. of dogs in Medan to be carriers, and the organisms were proved to be present in the kidney tissues. Very occasionally, human cases of infection by *L. canicola* have been found in Holland. Human cases from the bites of infected rats have also been reported.

Guinea-pigs are very susceptible to experimental infection, and so also, but to a lesser degree, are dogs and puppies, rabbits and monkeys. To produce the disease in these animals, 3–5 c.c. of the patient's blood is required, and should be injected intraperitoneally ; the animal dies of intense jaundice about the tenth day.

Pathology.—The liver is invariably increased in size, and may weigh 100–150 oz. The gall-bladder is generally half-filled with brown or greenish-brown bile. The various microscopic lesions are reducible to three main types. In the first there is little destruction of the parenchyma or intercellular tissue ; the second is characterized by extreme cellular degeneration ; in the third there is a localized destruction of glandular tissue. The fatty degeneration of the liver in Weil's disease is moderate and not so advanced as that seen in acute yellow atrophy. The leptospiræ can be demonstrated among the cells in large numbers by Levaditi's method. There is remarkable similarity between the pathology of this disease in man and in infected guinea-pigs. In the liver the cells appear to be killed individually, not in bulk. The spleen may be enlarged and the glandular substance soft and diffluent (about 12 oz.). A generalized enlargement of the lymphatic glands, especially at the hilum of the liver, with hyperplasia and multiplication of the mononuclear cells, has been noted.

Hæmorrhages occur in the kidneys, mostly in the intertubular tissues; later in the disease the microscopic picture may resemble that of early interstitial nephritis, and leptospiræ may be demonstrated in great profusion. The cells of the convoluted tubules are specially attacked. Blood escapes into the glomerular capsule and down the lumen of the tubule. There is said to be a reduction in the hæmoglobin and polymorphonuclear leucocytosis of 10,000 or more. There is also a reduction in the number of blood-platelets to 10,000 per c.mm. (normally 200,000). The coagulation-time of the blood is increased to twenty minutes.

Inoculated guinea-pigs and puppies show marked tendency to bleed; hæmorrhages into the lung impart a characteristic appearance, the so-called "butterfly lung," or "butterfly patches."

Symptoms.—The clinical symptoms can be divided into the first, or *febrile*, the second, or *icteric*, and the third, or *convalescent* stage. Sometimes the curious phenomenon of "*after-fever*" is observed. The *incubation period* in man, as well as in experimental animals, is from six to eight, seldom as long as thirteen days. The *onset* is acute, with rigors, vomiting, headache, diarrhœa, and abdominal pains, which may simulate acute appendicitis. A few hours later, fever ensues, with thirst and very severe general aching of the limbs. There is intense injection of the eyes, which may constitute the earliest and most striking feature and is almost pathognomonic; a distinct network of vessels is seen on the cornea and sclerotics. This reaction is believed to be due to primary invasion of the conjunctiva by leptospiræ. There is also a red plush-like injection of the soft palate, and often herpes labialis, which may be hæmorrhagic. The intense prostration, the almost agonizing muscular pains and aching of the bones, with hyperæsthesia of the calf muscles, as if the muscles were being cut through with a knife, constitute the most distressing features of the illness. The muscles themselves are very tender. The pyrexia is irregular, between 103° and 105° F., falling by lysis in severe cases about the tenth or eleventh day. There is usually a secondary terminal rise of temperature lasting three to nine days, which is associated witn excretion of leptospiræ from the urinary tubules. Convalescence is established in the third week, but there is sometimes a short temporary recrudescence of fever ("after fever"), which is thought to be an allergic phenomenon. Jaundice, which occurs in 50 per cent. of cases, is noted in from forty-eight to seventy-two hours from the onset, and may be ushered in by hæmorrhages into conjunctivæ or skin, or even from mucous surfaces. The skin is lemon- or orange-coloured, rarely greenish, pruritus being very frequent. The icterus is probably dependent on disorganization of function of hepatic cells, and is also due in part to hæmolytic icterus following destruction and phagocytosis of red blood corpuscles. The Van den Bergh reaction is therefore almost always biphasic. The jaundice becomes progressively deeper until the ninth or tenth day, but afterwards fades with great rapidity. From the fourth day onwards there may be rashes, morbilliform, erythematous or papular, over the loins, sides of the abdomen and below the scapulæ, symmetrically distributed. A purpuric rash betokens a bad prognosis. Large black hæmorrhagic spots are sometimes seen.

The urine is highly coloured, nearly always containing albumin and bile, and sometimes casts and red blood-corpuscles. The amount is reduced, and the albumin content may be considerable, and usually persists for seven to ten days, after which a trace only may be found. Bile pigments have been noted in the urine in patients without overt jaundice. The blood-urea is usually raised before the tenth day of the disease, and a secondary rise occurs during the secondary fever. The leptospiræ may be demonstrated in the urine from the tenth day to the twenty-fifth, and may persist as long as 63 days. They can rarely be recovered from the blood after the twelfth day.

Prostration may be extreme. Constipation is the rule, but the fæces contain abundant bile. The pulse is slow in the later stages, and the blood-pressure low. A polymorphonuclear leucocytosis, of 10,000 per c.mm. or over, is present with an Arneth " shift to the left " ; later there is an increase in the lymphocytes. A high blood-urea of 200–300 mgm. per 100 c.c. of blood is usually found, but is not necessarily serious. The liver may be enlarged, but splenomegaly is quite exceptional ; the gall-bladder is distended and tender ; the lymphatic glands, especially the inguinal and axillary, are often palpable and tender.

The *third* or convalescent stage begins on the thirteenth or fourteenth day with rapid subsidence of the icterus. The patient remains weak, anæmic and emaciated. During convalescence, guinea-pigs can still be infected by injection of urinary sediment.

Mild form.—After three or four days, in mild cases, the fever subsides by lysis. Slight or even severe febrile relapses are often seen at the beginning of the third week. Davidson (1937) and Sladen (1939) called attention to " subclinical " forms in those exposed to infection.

Varieties.—Typhoidal, uræmic, and meningeal forms—all of great gravity—have been described. In the typhoidal type there may be black vomit, delirium, and muscular twitchings. Insomnia is invariable. In the meningeal type, the cerebro-spinal fluid is under pressure, and contains excess of albumin and leptospiræ in large numbers. Murgatroyd has described a peculiarly chronic meningeal form in which the leptospiræ were recovered from the cerebro-spinal fluid six months, and from the urine eight months, after the onset of the illness. The patient recovered after intrathecal injection of antileptospiral serum. Mollaret and Erber have found that forms of leptospiral meningitis are comparatively common in France. Fatal cases are usually associated with paraplegia.

Complications.—Epistaxis, hæmaturia, melæna, hæmoptysis, deafness and pharyngitis have been noted as complications, and also inflammatory ocular changes, such as iritis and irido-cyclitis. The secondary fever (after fever) or recrudescence with rigors, may occur about the fourteenth or fifteenth day without recurrence of jaundice. During this stage a remarkable pyrexia may develop ; in Japan it is seen in 30 per cent., and in Europe in 40 per cent. of cases and may last 14–24 days. The height of the fever is often greater than during the first febrile stage. There are many arguments against the view that this fever is a relapse, as all attempts to infect guinea-pigs with blood have been negative. It is generally regarded as allergic, and due to absorption of toxins. The sequelæ are anæmia and debility. Alopecia usually occurs in convalescence.

The mortality-rate may be fairly high—in the Andaman Islands about 18 per cent.

Diagnosis.—The urine from the fifth to the eighth day gives an intense green reaction when one or two drops of acetic acid are added. Early in the disease, if possible before the third day, the blood should be examined under the dark illumination for leptospiræ, and in doubtful cases should be inoculated into guinea-pigs for confirmation. For this purpose 6 c.c. should be injected directly into the peritoneal cavity; citrated blood acts equally well, if not kept longer than twenty-four hours. The diagnosis may also be made, probably with more certainty, from the twelfth day onwards, by injection of the same quantity of catheterized urine. According to Fletcher, the diagnosis is most simply and readily made by direct inoculation of the blood into blood-agar, and subsequent incubation. Blanchard and Lefrou (1922) increased the chances of finding the parasite by triple centrifugalization of the blood. According to Schüffner, one centrifugalization of 10 minutes' duration at 1,500 revolutions is useful in demonstrating leptospiræ, when the plasma is separated from the precipitated red blood-corpuscles and then examined in a thick layer.

An agglutination test with cultures of leptospiræ grown on solid media is much used; it occurs in a titre of 1 in 500, 1 in 1,000, and even as high as 1 in 30,000 (Davidson, Schüffner *et al.*). The specific agglutinins appear in the serum as early as the sixth, more generally about the tenth day of the illness, and persist for as long as twenty-two months.

Postmus (1933) found that this property of the serum may sometimes persist for eight years or longer. In carrying out the test Schüffner used living cultures of leptospiræ, and also cultures killed and preserved in formalin (0·2 per cent.). A small amount of gentian violet may be added to facilitate the reading of the results. One drop of antigen and various dilutions of serum are mixed in squares ruled on a slide, rocked for ten minutes, and then examined on a white background in diffuse transmitted light. On the whole, the macroscopic agglutination test is less sensitive than the microscopic. For the macroscopic agglutination test the antigen is prepared from actively growing young cultures of leptospiræ. The volume of culture added is equal to six times the volume of each dilution of the serum tested. The mixture of serum and culture should be incubated for three hours at 37° C., followed by thirty minutes at 55° C. With living leptospiræ agglutination appears only in the lower dilutions, as in the higher lysis sets in, rendering agglutination impossible. The one disadvantage is that the formalin mixture after some weeks is rendered useless by matting together of the leptospiræ into felt-like clots. The agglutination-absorption test was used by Schüffner and others as a means of differentiating strains of pathogenic leptospiræ; by these means he separated *L. canicola* of the dog.

Brown and Davis demonstrated that the "adhesion" or Rieckenberg phenomenon is applicable to the diagnosis of Weil's disease as well as of trypanosomiasis. The reaction possesses distinct advantages over agglutination owing to the ease and certainty with which it can be practised. The test consists in allowing the immune serum to interact with the specific leptospira in the presence of a suitable indicator such as bacilli or blood-platelets. Not only can the disease be diagnosed by this method, but it may also furnish a means of differentiating leptospiræ.

The cultures used for the macroscopic agglutination test are obtained on Noguchi semi-solid medium by incubating at 32° C. for 5–7 days; 0·2 c.c. of such a culture of actively motile leptospiræ is kept in a water-bath for one and a half hours at 37° C., mixed with an equal quantity of antileptospiral serum and examined by dark-ground illumination for agglutination.

Gaehtgens a elaborated a complement-fixation test. The antigen is a culture of leptospiræ, centrifuged, and the sediment suspended in saline containing 0·3 per cent. carbolic acid.

The centrifuged deposit of urine rich in these parasites may be utilized for an agglutination test in place of a culture, and the diagnosis has by these means been placed upon a scientific, if not on a practical basis. The leptospiræ can usually be demonstrated in centrifuged urine, and may be present up to the sixty-third day, though they generally disappear on the fortieth. Davidson has pointed out that their numbers are somewhat inconstant and they may disappear altogether in acid urine. If negative at first, this test should be repeated every second day up to the end of the third week.

An antiserum specific for the *Leptospira icterohæmorrhagiæ* has now been prepared from rabbits, and by this means the identification of the organism has been made possible.

From the fifteenth day onwards the immunity reaction may be employed; for this purpose 1 c.c. of the patient's serum is left in contact, for fifteen minutes, with several times the lethal dose of the leptospira, and injected into a guinea-pig, which does not develop symptoms of the disease, while control animals die.

Differential diagnosis.—The disease has to be differentiated from yellow fever, infective hepatitis, catarrhal jaundice, syphilitic disease of the liver, and the icterus of relapsing fever and of malaria. The fever must be distinguished from that of relapsing and of yellow fever, and the leptospira from *Spirochæta recurrentis*. On clinical grounds the diagnosis should not be missed, when jaundice, associated with nephritis and nitrogen retention, is followed by headache, muscular pains and scattered hæmorrhages. The difficulty in differential diagnosis between leptospirosis and yellow fever may be realized when it is remembered that the cases studied by Noguchi as instances of yellow fever were, almost certainly, cases of leptospirosis. Faget's sign is not present in leptospirosis (*see* p. 338).

In fevers such as typhus and cerebro-spinal fever, and in several others in which relapse may occur, including plague, rat-bite fever, and paratyphoid (especially paratyphoid-B), jaundice may be a complication. Other possibilities are lobar pneumonia, portal pyæmia, and occasionally *Bact. coli* septicæmia.

TREATMENT

1. General conduct of the case.—The systematic treatment consists in keeping the patient at rest, flushing out the bowel by repeated small doses of calomel, and intravenous injection of normal saline containing 5–10 per cent. of glucose. Should the nephritic symptoms become e, intravenous injections of saline or of Ringer's solution, ½ to 1 litre, necessary. The diet must be liquid and, if vomiting is persistent, be given as nutrient enemata. For the pruritus accompanying icterus, spirit of camphor or mentholated vaseline is recommended.

2. Antiserum treatment.—The scientific treatment consists in the administration, as soon as possible, of a polyvalent antiserum which is prepared from horses injected with cultures of *L. icterohæmorrhagiæ*. An efficient serum is now prepared by Burroughs Wellcome. This is given intravenously at intervals of several hours for at least four days in succession; 20 c.c. at least should be given at each injection. For a man of 70 Kg. weight, the dosage is 60 c.c. daily for three to five days. Usually, after this treatment the temperature begins to fall, but in advanced cases, in which jaundice and uræmic symptoms have supervened, the method is of little value. Failing the provision of commercial anti-leptospiral serum, the serum of patients convalescent from this disease has been injected in daily doses of 30–40 c.c. intramuscularly. To give the best results, this immune serum should have an agglutination and lysis titre of 1 : 20,000, and this is reached 30–50 days from the commencement of the attack. It deteriorates when stored and should not be used after six months.

3. Other measures.—*Hexamine* has been recommended and *sodium tartrobismuthate* has given good results when injected subcutaneously. Uhlenhuth and Seiffert have recommended injections of Bismuth-Yatren A and B.

Prophylaxis.—Prophylaxis manifestly consists in sterilizing the fæcal and urinary discharges of the patients, and in waging war against the rat, the natural host of the parasite, and carefully guarding against its access to food. Swimming, especially the "crawl stroke," in pools or rivers known to be the source of the disease should be avoided. Sewer workers must protect themselves against abrasions. Noguchi prepared a vaccine of killed cultures of leptospira which he used for prophylactic inoculation in Japan.

SEVEN-DAY FEVER

Synonyms. Nanukayami; Shueki; Sakusku Fever (Japanese); Autumn Fever; "Pomona Fever" (Australia).

Definition.—A short fever, due to *Leptospira hebdomadis*, occurring epidemically during the summer months, especially in Japan (Fukuoka), characterized by sudden invasion, severe headache, pains in the back and limbs and pyrexia of a peculiar saddle-back, or occasionally of a continued type, lasting from six to seven days and associated with a relatively slow pulse.

History.—Possibly this is one of several fevers included under the term "simple continued fever." Its differential diagnosis from dengue was rendered clear by the discovery in 1918 of the *L. hebdomadis* by Ido, Ito, and Wani.

Geographical distribution.—The home of the disease is Japan, and it is found in China (Shan-si), and also in India, the Dutch East Indies and Australia, especially in dairy farmers. A disease of dogs in the Malay States was proved by Fletcher to be produced by a leptospira of the *L. hebdomadis* type (possibly identical with *L. canicola* of Schüffner, *see* p. 202).

Possibly the organism described by Derrick (1942) in Queensland as *L. pomona* is related to *L. hebdomadis*.

Ætiology.—*L. hebdomadis* resembles *L. icterohæmorrhagiæ* closely, but can be distinguished by serological reactions. The organism is said by Noguchi to be slightly longer, the elementary spirals almost geometrically equidistant. It is present, though in small numbers, in the blood-stream during the pyrexial period, may be demonstrated by Giemsa's stain or by the dark-ground illumination, and is readily cultivated by Noguchi's method. The chief channel of elimination is kidneys and urine.

The short-eared field-vole (*Microtus montebelloi*) appears to be the normal host of the leptospira in Japan, and the organism can be detected in the kidneys and urine of 3·3 per cent. of these animals, which can convey the disease by their bite. The endemic area of prevalence of seven-day fever corresponds with the distribution of this vole in Japan.

Microtus, sometimes termed a field-mouse, is really a stump-tailed field-vole, and is common in country districts in Japan. It burrows in the ground and feeds on roots and grain in much the same way as other small rodents.

The blood of convalescents from seven-day fever contains specific immune and leptospiracidal bodies and, when injected, together with a culture of the organism, into the peritoneal cavity of a guinea-pig, gives a positive Pfeiffer reaction. Young guinea-pigs are susceptible to inoculation with the blood of patients, and with cultures of the leptospira ; they may also be infected *via* the skin or *per os*.

Symptoms.—The symptoms resemble those of Weil's disease, and the blood shows a slight leucocytosis. The disease appears to be transmitted by the bite of infected field-mice, so that the patients are generally workers in the fields and forests.

After a short invasion-period the fever comes on briskly, and is accompanied by depression, muscular pains, especially in the calves, conjunctivitis, digestive symptoms, and enlargement of the lymphatic glands. Apparently, seven-day fever is a mild disease and has no mortality, and no distinctive pathological anatomy. The organism can be demonstrated in considerable numbers in the urine after the eighth day, and may persist to the thirty-ninth day. Albuminuria is noted in the early stages.

Differential diagnosis.—The disease is to be distinguished from relapsing fever, Weil's disease, rat-bite fever, and especially from dengue. There is considerable difficulty with dengue, for many writers have confused the two diseases, and some consider them identical, but in view of recent work there can be little ground for adopting this view. The bone-pains and the morbilliform eruption in dengue suffice to distinguish it from seven-day fever.

Treatment.—The disease being generally slight, no specific treatment has been evolved. The fever must be treated on general lines.

NOTE.—In Sumatra various observers have isolated leptospiræ from illnesses of different degrees of severity, including fevers of from one to five days' duration with no jaundice ; more severe cases with jaundice ; and finally, hæmoglobinuric cases resembling blackwater fever (*see* p. 74). The organism isolated from mild cases is morphologically identical with *L. icterohæmorrhagiæ* and may produce severe symptoms on inoculation into guinea-pigs. Vervoort (1923) proposed the name of *L. pyogenes* for organisms isolated from these fevers of short duration.

Fletcher in the Malay States also isolated leptospiræ from a variety of febrile cases, some resembling dengue, and he classified the organisms serologically into a number of groups. Owing to the instability of serological reactions, and the fact that primarily non-pathogenic water leptospiræ may be rendered pathogenic so as to produce symptoms of Weil's disease in animals, Baermann and Zuelzer reached the conclusion that all so-called pathogenic leptospiræ are identical with free-living forms in water. *L. icterohæmorrhagiæ* nd *L. hebdomadis* may therefore be identical.

CHAPTER VII

RAT-BITE FEVER

Synonyms. Sodoku—*so* (rat), *doku* (poison); Sokosha (Japanese); Cat-bite Disease.

Definition.—An acute febrile disease caused by *Spirillum minus* (*morsus-muris*), inoculated into man by the bite of an infected rat (sometimes also cat and ferret) causing a local disturbance at the site of infection, followed by a general fever, with a tendency to relapse and, in some cases, a cutaneous eruption.

History.—This disease has long been known to Japanese physicians. Since its recognition, cases have been reported from India and other countries. In 1915, Futaki, Takaki, Taniguchi, and Osumi demonstrated spirilla in the lymphatic glands from the tenth to the thirteenth day of the illness; later they found similar, though shorter and stouter, organisms in the blood-stream; the latter are now recognized as being the young forms of the parasite. This work has since been confirmed by Kaneko and Okuda in 1917, and by R. Row in Bombay. A. Robertson showed the organism to be a spirillum, and its correct nomenclature to be *Spirillum minus*, Carter 1887.

Geographical distribution.—Rat-bite fever appears to have a widespread distribution, but is especially common in Japan. Cases have been reported in Great Britain by Horder, Low, Atkinson, and Joekes, and from the United States, Germany, Italy, Australia, and East Africa.

Ætiology.—*S. minus*[1] is a short, squat spirillum differing greatly from spirochætes, at any rate in the human body. It measures 1·5–6 μ in length; the pointed extremities are continued into one or more flagella; including this, the total length may be 15 μ. (Fig. 37.) The curves are regular, and generally number three or four, or even six or more. It is difficult to demonstrate in the blood in the living state even by the ultramicroscope, but it may be seen in the exudate in the neighbourhood of the bite, and in the juice from the superficial lymphatic glands.

In the living state the organism, under the microscope, moves rapidly like a vibrio, by lashing movements of the flagella; the body itself is held rigid, and in this manner the movements can be readily distinguished from the vibratile motions of the true spirochætes. This fact, together with a certain amount of doubt regarding its method of multiplication, has led to some controversy on its systematic position. The presence of the spirillum can be easily verified in suspicious cases by inoculation of white mice with any of the material in which it can be seen. Next to mice, white rats and guinea-pigs and monkeys (*Macaca*) are most susceptible. The spirillum can also persist in the blood of dogs without giving rise to any obvious symptoms. In mice, Ozeki has shown that the infected animals can be recognized within one or two months after infection by the loss of hair on the belly and chest and the nasal line, including the eyes and ears. Usually, however, experimental animals survive. The organisms appear in the blood-stream about seven days after inoculation, and persist for several months. The disease can be transmitted by the brown rat (*Rattus*

---

[1] Formerly known as *Spirochæta morsus-muris.*

norvegicus), the black rat (*R. rattus* and *R. alexandrinus*), the bandicoot rat (*Nesokia bandicota*) and the ferret or cat.

In Calcutta 2 per cent., in Venezuela 10 per cent., in Amsterdam 1 per cent., and in Toulon 18 per cent. of rats have been found infected. *S. minus* has not been found in the rodent's saliva, but the transfer seems to take place by a breach in the tissues through which the organism escapes, and is thus inoculated into the bite wound.

The organism resembles, and is probably identical with, *S. laverani* and *S. muris*, which have been found in the blood of rats and mice in various parts of the world. Levaditi states that in mice this infection is hereditary. Saisawa and Taise have shown that the spirilla can be found in large numbers in the peritoneal fluid of mice, and when these animals are treated with small quantities of neosalvarsan the organisms persist in the brain and in the spleen. Like the true spirochætes, they have the power of forming remarkable agglomerations, sometimes forming balls 40-50 μ in diameter. Under the dark-ground illumination, these clumps move like a rolling ball.

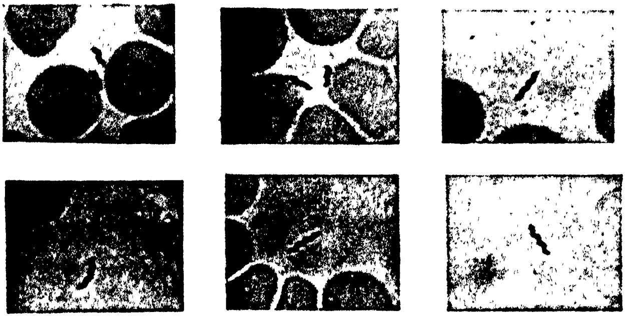


Fig. 37.—*Spirillum minus* **of rat-bite fever in mouse.** × 1,500.
(*Microphotograph : Dr. A. C. Coles.*)

Joekes has succeeded in cultivating *S. muris*, which he found in 25 per cent. of the wild rats in London, by using an inspissated horse-serum slope, as employed for the diphtheria bacillus, over which is poured Vervoort's medium (1 per cent. peptone to which are added 3 c.c. of normal phosphoric acid). Primary culture is obtained by inoculating the medium with blood from an infected guinea-pig and incubating at 37° C. Subcultures are easily maintained in 1 per cent. glucose broth.

The immunity conferred on man and animals by an attack of this fever is permanent, and protects, apparently, against all other organisms of the same type that have been procured from various sources.

Although the general belief is that *S. minus* is the cause of rat-bite fever, it is necessary to state that there are some cases from which *Streptobacillus moniliformis* can be isolated on special media. In the United States it has been found that infection of wild rats with *S. moniliformis* is much commoner than with *Spirillum minus*. By some this is still considered to be the ætiological agent.

S. moniliformis, first isolated in 1914, was shown by Parker to be responsible for a milk-borne epidemic, "Haverhill fever". Arthritic symptoms were common. It is recognized in the U.S.A. that there are two rat-bite fevers, and that the one due to *S. moniliformis* is curable by intramuscular injections of 200,000 units of penicillin.

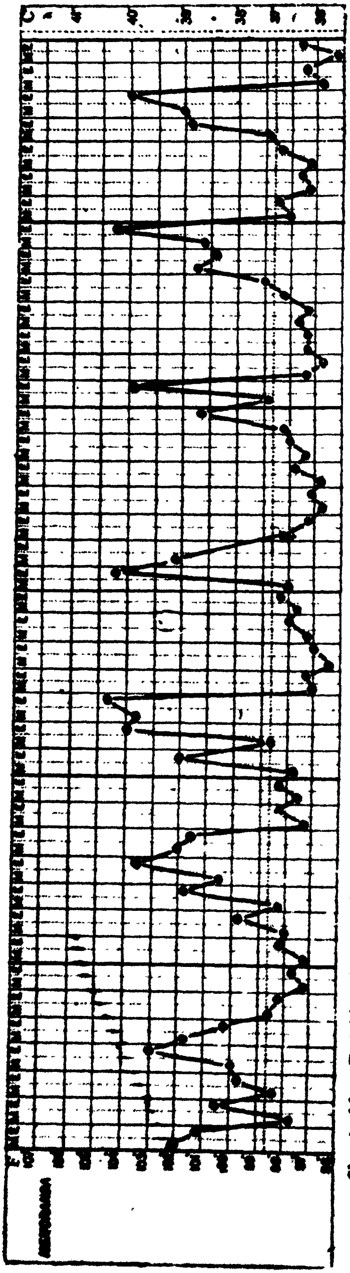


Chart 11.—Rat-bite fever, showing periodic relapses. (*By permission of London School of Hyg. and Trop. Med.*)

Pathology.—In inoculated guinea-pigs and white rats swelling of the lymphatic glands and spleen is observed. There have been few recorded human autopsies. Degenerative changes occur in liver and kidneys. In some cases increase of cerebro-spinal fluid and hyperæmia of the cerebral cortex have been reported.

Symptoms. — The *incubation period* varies from one to sixty days, the average being from five to ten days, during which time the wound heals. Then the cicatrix itself, and sometimes the surrounding tissues, become inflamed, with formation of blebs and even necrosis. The lymphatics draining the area are implicated, and the glands themselves become swollen and tender. The onset of the fever is characterized by rigors and malaise; the temperature gradually rises in three days to a maximum of 103–104° F., and, after a further period of three days, ends in crisis with profuse sweating.

After the primary attack a quiescent interval of five to ten days ensues, with subsidence of the local disturbance. One or more relapses (Chart 11), associated with the same symptoms and a characteristic purple papular exanthem or urticaria on the chest and arms, have been noted. The eruption is sometimes nodular. With each bout of fever the cicatrix at the site of the original bite becomes inflamed.

In most cases the reflexes are increased; there may be pains in the muscles and joints, and hyperæsthesia and œdema of various parts of the body. In some cases arthritis has been reported. The death-rate is about 10 per cent. In fatal cases the end is ushered in by delirium, often lapsing into coma. Some cases subside spontaneously: others go on for months.

As in relapsing fever, the organism can be demonstrated in the blood during the fever only, disappearing during the apyretic intervals. The serum agglutinates the spirillum in low dilutions. There is an eosinophilia during the paroxysm and a moderate leucocytosis of about 15,000. It is said that the serum in this disease gives a weak positive Wassermann reaction.

Diagnosis.—In many cases the diagnosis of rat-bite fever can be fully established from the history, the infiltration at the seat of the bite, the typical temperature curve, the rash, and the effects of the administration of salvarsan. This diagnosis can be confirmed either by dark-ground illumination, when spirilla may be seen in the exudate obtained from the site of the bite, or in the serous fluid from the papule, or by Giemsa-stained smears. It is seldom possible to demonstrate spirilla in a thick blood-film. If a number of relapses have occurred, probably the best examination to make is for the presence of lytic antibodies. Absolute proof of the clinical diagnosis may be obtained by inoculating the patient's blood, lymph gland, or a piece of excised wound into guinea-pigs and mice.

Savoor and Lewthwaite demonstrated the curious fact that a well-marked rise in Proteus OXK agglutinins occurs in the blood of rabbits inoculated with *S. minus*, but in man, as well as in infected monkeys, the reaction is negative.

Differential diagnosis.—This has to be made from the different forms of relapsing fever and trench fever, with which the temperature chart has much in common. In tropical countries the possibility of a co-existent malarial infection has to be taken into account. The puffiness of the face accompanying the urticarial eruption may simulate Bright's disease.

The reaction occurring around the site of the scar is apt to be confused with erysipelas or cellulitis.

Treatment.—Salvarsan and its derivatives act as a specific. As a rule, one injection of neoarsphenamine[1] (0·4 to 0·6 grm.) is sufficient to cure.

Occasionally the intravenous injection has to be repeated as a prophylactic measure. Schoekaert has shown that antimony preparations, especially *stibosan*, given in therapeutic doses, are effective in rat-bite fever; on the other hand, tartar emetic and antimosan have no effect on the spirillum. A cat- or rat-bite should always be cauterized.

As in syphilis (*Spirochæta pallida*), so in rat-bite fever the bismuth compounds appear to have a definite curative value. Montel and Truong-Van-Que have advocated *Bivatol*, which they have given intramuscularly at intervals of three and five days. Two cases were completely cured after four intramuscular injections. Stovarsol tablets are also credited with curative properties.

Prophylaxis.—Quite obviously, the prophylaxis of this disease, as in plague, rests upon efficient rat destruction. In Manila, for instance, it has been found that the distribution of rat-bite fever and plague are co-extensive and that therefore measures taken against one are in fact effective against the other.

---

[1] Neoarsphenamine is the name officially adopted in place of novarsenobillon, neosalvarsan, etc.

Subsection C.—FEVERS CAUSED BY BARTONELLA AND RICKETTSIA BODIES

CHAPTER IX

BARTONELLOSIS

(OROYA FEVER AND VERRUGA PERUANA)

MEDICAL opinion in Peru has always regarded Oroya fever and verruga peruana as clinical manifestations of the same disease. For a time this view appeared to be negatived by the Harvard Commission in 1915, but the important work of Noguchi on the cultivation of the virus of Oroya fever, and the subsequent production of verruga-like lesions on inoculation into monkeys, has established the unity of these apparently distinct diseases as generalized and localized manifestations of the same infection. Mayer and Kikuth in Germany fully confirmed the work of Noguchi.

OROYA FEVER STAGE (GENERALIZED BARTONELLOSIS)

Synonym. Carrion's disease.

Definition.—An acute specific fever, endemic in certain valleys of the Andes, characterized by a rapidly developing anæmia of the pernicious type, irregular pyrexia, and great tenderness over the blood-forming tissues. The organism is *Bartonella bacilliformis*.[1]

History.—The first attempt to settle the ætiology of this disease was made by the self-sacrifice of Carrion, a medical student who, in 1885, fatally inoculated himself with the blood from a verruga nodule in Lima. From this experiment Peruvian physicians concluded that the verruga and Oroya fever were different stages of the same disease. Many thousands died of this fever during the reign of the Inca, Huayna Capac.

It is thought that Oroya fever was the disease which proved so fatal to Pizarro's army in the sixteenth century. Bours has recorded that all engineers superintending the building of the Trans-Andean railway contracted fever and half of them died of it. In 1906, out of 2,000 men employed on tunnel work, 200 perished. The monograph of Odriozola (1898) contains a classical account.

Geographical distribution.—Between the 9th and the 16th parallels of South latitude, and at an elevation of from 3,000 to 10,000 feet, in certain narrow valleys (quebradas) of the western slopes of the Andes, this peculiar fever is endemic. It is therefore found in Peru, Ecuador, Bolivia, Colombia, and Chile, and probably in Guatemala. A considerable outbreak occurred in the Guáitara Valley in South Colombia, near the Ecuador boundary, in 1936. Its topical as well as its geographical range is singularly limited; it is confined to certain hot, narrow valleys or ravines, the inhabitants of neighbouring places being exempt.

It is said that the disease may be acquired when merely journeying through the endemic districts, more especially if the traveller passes the night there. Although out-of-door workers are the most subject, all ages, classes, and both sexes, including infants, are liable.

---

[1] *See* the authoritative work, *Infectious Anæmias due to* Bartonella a D. Weinman, *Trans. Amer. Phil. Soc.*, 1944, XXIII, Part III, 243-339.

Ætiology.—During the fever certain rod-like bodies are found in a large proportion of the red blood-corpuscles (Fig. 38), and in endothelial cells of the lymphatic glands. These were first noted in 1905[1] and again in 1909 by Barton who considered them protozoal; his findings were subsequently confirmed by Strong and other members of the Harvard Commission, who termed the bodies *Bartonella bacilliformis*. The organisms somewhat resemble stages of a piroplasm (*Theileria parva*) during its cycle in the lymphatic glands, and similar bodies are found in the blood of normal mice and certain rodents (*Bartonella muris*), which, as Mayer, Borchardt and Kikuth have shown, exist as a latent infection, but which may produce an acute and fatal anæmia, resembling Oroya fever, after removal of the spleen. The causal organism of dog-anæmia following splenectomy is *Bartonella canis*. The clinical course of this infection is connected with an endothelial reaction, and the organism is transmitted by rat-lice (*Hæmatopinus*).

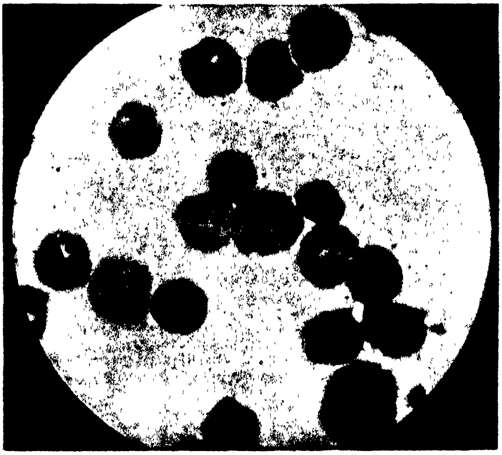


Fig. 38.—Blood smears with numerous *Bartonella bacilliformis* **(human Oroya fever).**

From the morphological standpoint, Bartonella and Rickettsia have resemblances. Both are minute, pleomorphic, Gram-negative and intracellular. On account of their peculiar behaviour, *Grahamella*, first described by Graham-Smith in the blood of moles, should be kept apart from *Bartonella* and regarded as a separate genus. In some respects they resemble *Bact. tularense*.

Two forms of *B. bacilliformis* are recognized: one is a rod-shaped, slightly curved bacillary organism 2 μ long by 0·5 μ broad, staining with Romanowsky an intense blue, often in branching forms and in chains, but never crossed; the other is a rounded body about 1 μ or less in diameter, usually oval or pear-shaped, and containing chromatin granules. Some occur singly, or end to end, in pairs or chains. V forms probably represent dividing organisms; Y shaped forms are also not uncommon. They are difficult to distinguish in fresh blood, and show feeble independent movement.

Noguchi regarded *Bartonella* as a bacillus and succeeded in cultivating it on solid media from specimens of citrated blood sent in "cold storage" from Lima to New York. The organism grows best at low temperature on blood-agar media. He was so successful in culture of the organisms that he recommended it in diagnosis as preferable to examining blood smears.

Battistini's method of culture is simple. A small drop of blood from the finger of the patient is withdrawn into serum-agar, or Noguchi's leptospira medium. The end is sealed in the flame and the whole placed in the incubator at 28° C. Colonies are visible in 5–6 days. *B. bacilliformis* is also readily cultivated in the allantoic fluid of the developing chick embryo at 25–28° C. The growth is rapid and abundant. The cultivated bodies are 0·6–1·6 μ in length. Weinman and Pinkerton (1938) preferred the agar slant method devised by Linsser for cultivation of rickettsia. The *Bartonella* is an obligatory aërobe and Gram-negative, but stains well with Giemsa. Intravenous injections of cultures into *Macaca* monkeys produce irregular fever and extreme anæmia; the organisms can be demonstrated in the blood-cells. Intradermal injection into the supraorbital tissues gives rise to nodules resembling verruga. In excised nodules *Bartonella* survives for at least fifty-six days at 40° C. Noguchi succeeded in conveying the infection to monkeys by the bites of ticks (*Dermacentor andersoni*) but Townsend in 1913 conjectured that the insect vector was a sandfly (*Phlebotomus verrucarum*). Further evidence incriminating *P. noguchii* and *P. verrucarum* was obtained by Noguchi and others in 1929, and this was confirmed in 1937 by Pinkerton and his colleagues. Insects were collected in a verruga district of Peru and sent in sealed glass tubes to New York. They were then ground up in saline and the emulsion injected intradermally into monkeys. The only insects which showed any evidence of containing bartonella were phlebotomi.

Hertig conducted transmission experiments in the laboratory with wild-caught phlebotomi from endemic zones. Five monkeys bitten by sandflies (*Phlebotomus verrucarum*) became infected with *B. bacilliformis.* As the result of extensive field studies on three species of phlebotomus, conducted for more than four years at different places and altitudes in Rimac and Santa Eulalia Valleys, it now appears that *P. verrucarum* (not *P. noguchii*) is the most important transmitter.

Hertig has also described a curious infection of the tip of the proboscis in both males and females of *Phlebotomus* captured in the Peruvian verruga zone. From these *B. bacilliformis* has been recovered by culture and also an unnamed micro-organism of similar morphology. The proportion of sandflies so affected may be from 40–50 per cent. In many instances the pharynx of the sandfly is also infected. Since this condition has been found in male insects which do not suck blood, as well as in females which have never had a blood meal, the possible relationship to Carrion's disease remains obscure.

The Neill-Mooser scrotal reaction is produced sometimes by inoculation of guinea-pigs with blood of Oroya fever or with cultures of *B. bacilliformis.* If present, it is well-marked on the third day.

The disease is most prevalent from January to April, when the streams are in flood, the air hot, still, and moist, malaria epidemic, and insect life abundant.

Pathology.—A remarkable feature of this disease is the rapid and extreme blood destruction. In bad cases the blood-count may drop in three or four weeks to 500,000 per c.mm., the picture being that of a pernicious anæmia. There is a marked polymorphonuclear leucocytosis with disappearance of eosinophils. The red cells are of the megalocytic type.

In addition to the anæmia, marked changes are present in the liver, spleen, and bone-marrow. In the liver, areas of degeneration and central necrosis are found around the hepatic veins. In the centre of the necrotic areas a yellow pigment resembling hæmosiderin is present in abundance.

The spleen is invariably enlarged, and also contains necrotic areas with pigment in the pulp, but the Malpighian bodies themselves are not affected. The lymphatic glands contain large macrophage endothelial cells studded with rod-shaped bodies. *B. bacilliformis* occurs in closely-packed masses in swollen endothelial cells, especially of the lymphatic glands, spleen, liver and intestines. The lesions in the viscera are considered by Strong to be due to toxins liberated by the parasite. The bone-marrow shows proliferation, necrosis, and marked phagocytosis of the large endothelial cells. Noguchi observed in monkeys succumbing to bartonella infection the same lesions as have been recognized in man—in the spleen and also in the lymphatic glands, endothelial cell hyperplasia ; in the bone-marrow an increase of macrophagocytes, and in some instances, normoblasts.

Symptoms.—The *incubation period* of Oroya fever is about three weeks. Its *onset* is insidious and is marked by malaise, soon followed by a rapidly developing pernicious anæmia and an irregular remittent pyrexia, associated with very severe pains in the head, joints, and long bones. The bone pains are probably connected with the disturbances in the hæmopoïetic system. Very often the initial fever is like that of a malaria infection, and may be the outcome of a double infection in a malarial subject. The most severe types resemble fulminating typhus and are known as the " severe fever of Carrion." The liver and spleen are enlarged and tender. The anæmia develops with great rapidity. The death-rate varies from 10 to 40 per cent. of those attacked, the end coming within two or three weeks of the onset of the disease. A terminal delirium is often noted. In those cases which progress to the verruga stage, the fever may last three to four months.

The Harvard Expedition to Peru in 1937 recognized three types of Carrion's disease.

(1) the anæmic ;
(2) the asymptomatic ; and
(3) the cutaneous, reproduced by inoculation of (*a*) infected lymph-nodules, (*b*) human verruga tissue, (*c*) cultures of Bartonella.

Treatment.— Kikuth produced an arseno-antimony compound, *Sdt.* 386 *B*, which is said to have a selective action for *Bartonella*. The therapeutic index is very high and the margin between the *dosis tolerata* and *toxica* is wide. Manrique reported results in twelve severe cases treated with intravenous doses of 0·1–0·3 grm. repeated two to three times. He succeeded in banishing *Bartonella* from the blood-stream and bringing about a rise in the blood-count. A total of up to 5–7 grm. of this drug was injected without causing any systemic disturbance. The general opinion of Peruvian physicians is that severe infections are not influenced either by this method or by blood transfusion.

VERRUGA PERUANA STAGE (LOCALIZED BARTONELLOSIS), OR ERUPTIVE STAGE

Definition.—A remarkable granulomatous eruption confined to certain parts of Peru, Columbia and Ecuador (Montalván and Moral, 1940). It is associated with hæmorrhages, fever and joint pains. The disease was known to Pizarro, and is described in Prescott's " Conquest of Peru."

Ætiology.—Superficially, the lesions of verruga resemble those of yaws.

Rocha Lima, Mayer, and Werner described chlamydozoa-like cell inclusions in the verruga nodules and considered them to be the cause of the disease. As already related, Noguchi demonstrated bartonella bodies in experimentally-produced lesions in monkeys. This work was confirmed by Mackehenie, Weiss, Mayer and Kikuth, who produced nodules in monkeys with human material and demonstrated Bartonella bodies within angioblasts or endothelial cells. Verruga is therefore a local connective-tissue infection with *Bartonella bacilliformis.*

Strong's experiments on monkeys showed that graduated inoculation of verruga material induces an artificial immunity. Verruga can be conveyed by inoculation to rabbits and dogs and, according to Townsend, occurs as a natural infection in native Indian dogs.

Pathology.—Primarily, the pathological changes consist in proliferation of the endothelium of the lymphatic channels, which become obstructed by plasma-cells and fibroblasts, but the structure is much more vascular than that of yaws, which it otherwise resembles. The capillary blood-vessels become dilated, so that the granulomatous tumours are vascular, almost cavernous, and apt to bleed profusely. A feature of the pathological histology is the formation around the blood-vessels of nodules of angioblasts characteristic of the disease. In the endothelial cells of cutaneous verruga nodules *B. bacilliformis* may be seen in considerable numbers, but distension of the cells is less than that seen in Oroya fever cases (Jiminez and Buddingh). Bartonella bodies may be found in the blood-corpuscles after prolonged search (Mayer), but in monkeys, if the spleen be removed, they multiply exceedingly and produce Oroya fever.

Symptoms.—The period of incubation subsequent to Oroya fever is thirty to forty days, but in those cases in which the initial fever is absent it is at least sixty days. Although verruga is usually a sequel of acute bartonellosis, it may arise spontaneously and independently of Oroya fever. The initial stages are characterized by peculiar rheumatic-like pains, together with fever, the pains being apparently like those of yaws, only more severe. As in yaws, the constitutional symptoms subside on the appearance of the skin lesion. The eruption, like that of yaws (*see* p. 586), may be sparse or abundant, discrete or confluent. As in yaws, individual granulomata may fail to erupt ; others may subside rapidly ; yet others may continue to increase, and then, after remaining stationary for a time, gradually wither, shrink, and drop off without leaving a scar.

The eruption is generally described as of two types, miliary and nodular —the former not exceeding the size of a small pea ; the latter, the rarer, less numerous, but consisting of much larger nodular masses. The miliary eruption, as a rule, is found most abundantly on the face and extensor aspect of the extremities, less commonly on the trunk (Fig. 39). A pink macule first appears, which later darkens and becomes nodular. These nodules may be flat or somewhat pedunculated. The verruga artificially produced in monkeys by injection of bartonella bodies is bright cherry-pink.

In yaws we find no mention of fungating granulomata in any situation but the skin. In verruga it seems that these vascular lesions may develop on mucous surfaces—in the mouth, œsophagus, stomach, intestine, bladder, uterus, and vagina. Hence the dysphagia—a common symptom—and occasional hæmatemesis, melæna, hæmaturia, and bleeding from the vagina. Relapses both of the fever and of the eruption may occur.

In inoculated monkeys swelling of the lymph-glands is an early and constant symptom.

The nodular eruption is more chronic than the miliary. Individual lesions may grow to the size of a pigeon's egg; they may become strangulated, and a source of danger from hæmorrhage. This type does not invade the mucous membranes, and is usually confined to the regions of the knees or elbows. It appears in crops, and lasts two or three months.

In contrast to Oroya fever, the mortality from verruga is practically nil.

Diagnosis.—The appearances of verruga are so characteristic that it is hardly likely to be mistaken for any other disease. Conceivably, it may resemble the frambœsiform eruption of secondary yaws; it may also be simulated by multiple warts, molluscum contagiosum, multiple fatty tumours (Dercum's disease) and, according to Strong, it is closely allied to, if not identical with, Bassewitz's angio-fibroma cutis conscriptum contagiosum. Individual tumours may resemble fibro-sarcoma or angioma. The Oroya and verruga stage frequently co-exist.

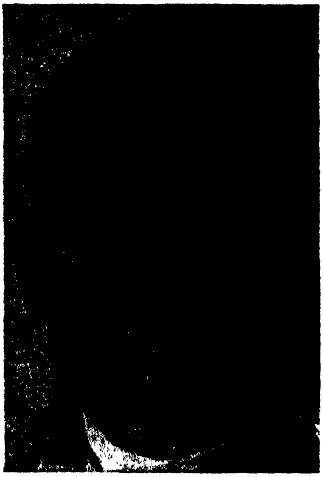


Fig. 39.—Verruga peruana. (*After Odriozola.*)

Agglutination reaction.—Suspensions of *B. bacilliformis* are obtained on media devised by Geiman. Sera from patients were found by Howe to agglutinate the organisms in titres from 1 : 10 to 1 : 80 in both the Oroya fever and verruga stages. A co-agglutination is usually found with cultures of *Proteus* $OX19$, OXK and OX_2. A strong agglutinating serum for testing cultures of *B. bacilliformis* has been produced by intravenous injection of rabbits with living cultures.

Treatment.—Very little is known about the treatment of this condition. Small doses of salvarsan, 0·2 grm. intravenously, have been tried with benefit. Intravenous injections of Kikuth's *Sdt.* 386*B* are recommended, in doses of 0·1–0·3 grm. repeated two or three times, but Strong was not at all impressed with the results. When individual tumours begin to ulcerate, or become gangrenous, they should be excised. Dangerous bleeding may occur, and styptics or compresses may be required to stay excessive loss of blood.

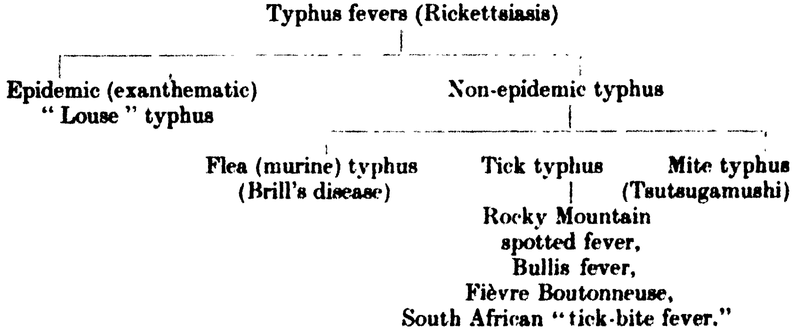
CHAPTER X

THE TYPHUS GROUP OF FEVERS

Preliminary statement.—Typhus fevers have an almost worldwide distribution, do not manifest themselves as one definite entity throughout their range, but are divisible into a number of local forms which have become stabilized in type. These forms, or varieties, are probably adapted to local conditions or in some way connected with those arthropod intermediary hosts which convey the virus. The student who is interested in the romance of this interesting subject should consult Zinsser's Rats, Lice and History (1935).

Classical typhus should be called " true " or " exanthematic typhus " and the local varieties should be known by their descriptive pseudonyms—Brill's disease, Tsutsugamushi, Rocky Mountain spotted fever, Fièvre boutonneuse, etc.

The following primary classification somewhat clarifies the situation :


Typhus fevers (Rickettsiasis)
Epidemic (exanthematic) " Louse " typhus
Non-epidemic typhus
Flea (murine) typhus (Brill's disease)
Tick typhus
Rocky Mountain spotted fever, Bullis fever, Fièvre Boutonneuse, South African "tick-bite fever."
Mite typhus (Tsutsugamushi)

Ætiology of the group.—*Rickettsia* are Gram-negative bacteria-like bodies, usually less than 0·5 μ in diameter. There are at present six named species and several varieties. The organism originally named *Dermacentroxenus rickettsii* by Wolbach, first described by Ricketts (1910), and now known as *Rickettsia rickettsii* is the causal agent of Rocky Mountain fever. The rickettsia of exanthematic typhus was named *R. prowazeki* by da Rocha-Lima (1916) in honour of two distinguished investigators (Ricketts and Prowazek) who both succumbed to the disease. Prowazek was the first to recognize the true nature of these organisms. Topfer (1916) described rickettsia in lice removed from patients suffering from Volhynian fever (trench fever) and this is now known as *R. quintana* (*R. volhynica*). Sellards (1923) distinguished the organism of tsutsugamushi disease in Japan as *R. orientalis*. The organism of flea-typhus is *R. prowazeki*, var *mooseri* (also *R. muricola*). The rickettsia of " Q fever," *R. burneti*, a comparatively recent discovery by Burnet and Freeman (1935), has a wide range in Australia and in North America, and is of much greater importance than was at first realized. The animal reservoir in Australia is the bandicoot, and the virus is conveyed to man by ticks. The reservoir of infection in America is as yet unknown.

Rickettsiæ are found commonly in the alimentary tract of blood-sucking and non-bloodsucking insects but, probably, they were primarily parasitic in the cells lining the canal. Thus, *R. pediculi* is an extracellular organism which is an inhabitant of the gut of the louse, is harmless to its host and also to man. In this respect it resembles *R. quintana* which develops in the same way and place.

The cycle of development of *R. prowazeki* in the louse consists primarily of great multiplication in the midgut, both in the lumen as well as inside the epithelial cells, which become distended so that they can easily be recognized. After a few days these cells rupture and rickettsiæ appear in large numbers in the fæces. This rickettsial invasion kills the louse in about ten days. The blood of typhus patients is infectious towards the louse from early in the disease up to the tenth day—occasionally later, even when the patient is afebrile. The disease therefore is conveyed to man by louse fæces through abrasions in the skin, or even through the conjunctiva ; possibly also by inhalation. Louse fæces kept dry at room temperature have been proved to be infective for 66 days. There is no hereditary transmission, and louse eggs do not contain the virus. A possibility exists that " clean lice " may themselves be contaminated by the excreta of other typhus-infected individuals.

R. prowazeki, var. *mooseri* (*R. muricola*) is normally transmitted from rat to rat by the rat louse (*Polyplax*) and by fleas. In these insects the cycle is similar to that already described in the louse. The species of flea mostly concerned is *Xenopsylla cheopis*, but in this instance the infection causes no appreciable harm to the insect host. In the fæces of the flea rickettsiæ remain alive and virulent for long periods—40 days in the dark and 100 days *in vacuo*. Zinsser and other authorities regard flea typhus as the original pristine form of human typhus.

The cycle of development of rickettsiæ in ticks follows on much the same lines, but is much more widespread. The rickettsiæ invade the cells and their nuclei and are found in all tissues, including the ovaries of the female tick, so that the infection is transmitted hereditarily. Rickettsiæ are also found in the salivary glands so that infection is commonly conveyed by the bite of the arthropod. The similarity of the clinical appearances of various forms of tick-borne typhus is undoubtedly close in widely separated geographical regions. In only one particular can they be said to differ—in the absence of a primary lesion in Rocky Mountain spotted fever and its presence in other types.

Zinsser has pointed out the importance of the hereditary factor of tick-transmission as indicating a very ancient condition, producing a mutual tolerance, so adjusted that neither the well-being of the animal reservoir or of the tick intermediary is impaired.

The mode of transmission of the rickettsia virus from animals to man, or from man to man, and the relationship of the various forms of typhus to one another can be expressed as follows :

Epidemic exanthematic typhus ..	Man—Louse—Man.
Murine Typhus (Brill's Disease) ..	$\text{Rat}\left\{\begin{array}{l}\text{Rat Flea}\\ \text{Rat Louse}\end{array}\right\}\text{—Rat.}$ Rat—Flea—Man. Rat—Flea—Man—Louse—Man (Probably)
Tsutsugamushi (Mite Typhus)	Rat or Field Mouse—Mite—Man.
Spotted Fever Types (Rocky Mountain Spotted Fever). "Tick Typhus." Fièvre Boutonneuse. S. African tick-bite fever	Rodents (Gopher)—Tick—Tick—Man Dog—Tick—Tick—Man.
Q Fever	Bandicoot—Tick—Tick—Man.

Morphology.—In their morphology in human tissues (Wolbach and Todd) rickettsiæ appear as small bacilli or cocci, very variable in arrangement. Diploid forms and also coccoid forms in dense masses are common. With the possible exception of *R. orientalis* they stain well by Giemsa's

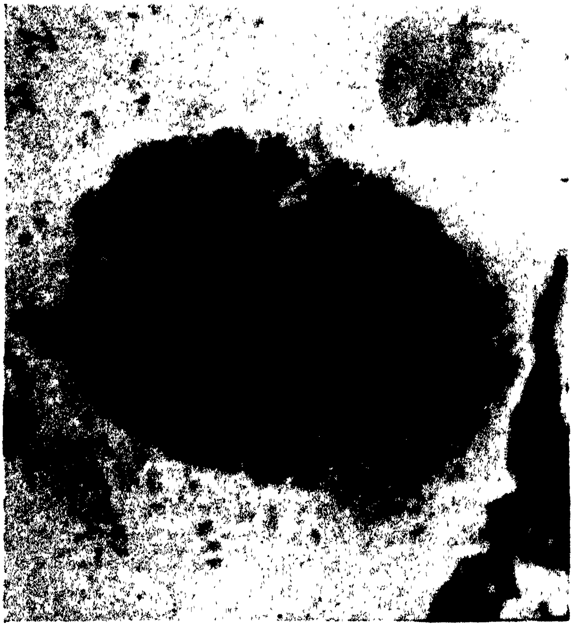


Fig. 40.—*Rickettsia prowazeki*, var. *mooseri*.
Tunica vaginalis of guinea-pig infected with murine typhus from wild rats. Cytoplasmic rickettsiæ invading a mononuclear cell. Giemsa stain. *Approx.* × 4,000 (Anigstein and Bader. Galveston, Texas).

method, and blue with Castañeda's stain (Fig. 40). None of the species can readily be cultivated on solid media (p. 223). Practically pure strains of *R. prowazeki* are obtained by intrarectal injection of lice with infected material, as practised by Weigl, but attempts to culture them from human tissues has so far been unsuccessful. All rickettsiæ grow readily on the chorio-allantoic membrane of the developing chick, and Gispen (1941) has shown that ducks' eggs are most suitable. The virus does not cause death of the embryo though the rickettsiæ produce big, round, prominent foci five days after inoculation and develop completely in 7–8 days. They grow in tissue cultures and in Maitland medium of minced chicken embryo in a mixture of guinea-pig or rabbit serum and Tyrode solution.

In all laboratories in which work is done with typhus rickettsiæ all workers are liable to attack, in spite of previous inoculation, so that vaccine cannot completely protect against the infection by the respiratory route that occurs in these cases, though it greatly reduces the severity of the attack.

Such an outbreak has now been reported in London by Van den Ende and others. Eleven cases could be attributed to inhalation of infective droplets during intranasal innoculation of mice under ether anæsthesia. In the remaining cases dust may have been the source of infection.

The metabolism of rickettsiæ differs from that of pathogenic bacteria in the fact that multiplication depends on the presence of living tissue. In this respect they resemble the true viruses. With the exception of *R. burneti*, the agent of Q fever, all pathogenic rickettsiæ are non-filterable. On these characteristics we are justified in placing rickettsiæ as intermediate between bacteria and true viruses.

Pinkerton has pointed out that the two main forms of typhus—the louse-borne and the tick-borne, may be differentiated by cellular reactions.

Exanthematic typhus, conveyed by lice and fleas, usually during the winter months, is characterized by invasion of the endothelium and mesothelium by rickettsiæ, producing distension of the cytoplasm of the host cells without affecting the nuclei, while in guinea-pigs it causes proliferative endangitis without thrombonecrosis. In typhus-infected lice and fleas rickettsiæ are intracytoplasmic, inhabiting the lining cells of the gut, and not hereditarily transmitted.

The *spotted fever group*, conveyed by ticks, is characterized by thrombonecrosis of arterioles and venules. The rickettsiæ in human tissues invade smooth muscle cells, endothelium, mesothelium and histiocytes. In *tissue-cultures* a massive infection of the nuclei takes place. In infected ticks the organisms are *intranuclear* as well as intracytoplasmic, invading nearly all types of tissue, and are hereditarily transmitted. These are suggestive distinctions.

Differential reactions.—The *Neill-Mooser reaction* is a distinctive reaction in guinea-pigs inoculated with typhus blood. A redness and swelling of the scrotum appears, and typical typhus lesions are found in the scrotal vessels, mostly in the endothelial lining of the tunica vaginalis ; swollen cells packed with rickettsiæ are seen in sections. Some strains, notably *R. rickettsii*, give this reaction more strongly than others ; it is also present in about 70 per cent. of exanthematic typhus and nearly always in the murine type. Raynal and Fournier have pointed out that a somewhat similar orchitic reaction may be caused by *Bact. paratyphosus B.*, and also by *Spirillum minus*, but the reaction occurs later, is harder and lasts longer.

AGGLUTINATION REACTIONS AS A MEANS OF DIFFERENTIATION

Serological division of the typhus fevers has been rendered possible by the introduction of the Weil-Felix reaction. This agglutination with cultures of *Proteus vulgaris* has been established since 1916. The original strain was known as *X*19; since then variants have been introduced which give different reactions with different varieties of the typhus group, e.g., *XK* (K for Kingsbury) X_2, X_3. On the whole, *X*19 is distinctive for exanthematic and murine typhus, XK for the mite-borne form; the others are indeterminate. It must, however, be remembered that, as the basis of this test is not yet understood, the exact implication of the results is insecure. (The agglutinins are present only in the human subject; they are not found in rickettsia-infected guinea-pigs.) *O* variants of the culture are used for agglutination—hence the prefix (e.g. *OX*19).

For the purpose of this test a drop of patient's serum is placed on a glass slide, mixed with a drop of blue (methylene blue)-tinted suspension of *Proteus OX*19 or other strain suitably diluted. When the reaction is positive, blue clumps appear within one or two minutes and are easily visible to the naked eye. Dried whole blood may also be used and, when subsequently extracted with normal saline, retains its agglutinating powers. The dry-drop blood tests can be carried out within a few minutes under primitive conditions.

The classification of the typhus group on the basis of host vectors has been adopted as a measure of convenience, but Felix asserted that satisfactory classification should be based solely upon the antigenic type of the corresponding rickettsiæ upon which immunity and immunological reactions depend. This can, however, not be accomplished until antigenic analysis of the various typhus rickettsiæ has been undertaken. *R. prowazeki* possesses a heat-labile as well as a heat-stable antigen, the latter being common to *R. prowazeki* as well as to *Proteus OX*19 and, further, this O antigenic compound is alkali-stable. The antigenic structure of the rickettsiæ of other types has not yet been studied owing to the difficulty of obtaining pure suspensions. This has now been overcome by the discovery by Cox and Castañeda of methods of growing these organisms in the yolk sac of the developing chick and in the lungs of infected mice and rats.

So far, the serology of the typhus group has been based on the antigenic relationship between the rickettsiæ of the different varieties of the disease and corresponding serological varieties of *Proteus X* (*OX*19, OX_2 and *OXK*), which has led to the subdivision of the typhus group into three immunological subgroups. Felix has further demonstrated that parts played by the two rickettsial antigens in typhus immunity are similar to those played by the Vi and O antigens in immunity to typhoid fever.

I. EPIDEMIC OR EXANTHEMATIC TYPHUS

Synonym.—True or classical typhus; Tabardillo = Burning Fever (Mexico).

Definition.—An acute fever, louse-borne, abrupt in onset, lasting about fourteen days and, if not fatal, terminating by crisis about that time. The pyrexia is remittent. On or about the fifth day there appears a roseolar eruption tending to petechiæ, spreading from the abdomen

over the trunk and extremities. As was stressed by Zinsser and MacArthur, typhus must be considered the most important disease in history.

Geographical distribution and epidemiology.—Epidemic typhus has an almost worldwide distribution. It is especially common on the Eastern Marches of Poland, North-West Soviet Russia and the Ukraine. Tarasevitch estimated that between 1917 and 1923 there were over thirty million cases with over three million deaths within the confines of European Russia. It is commonly encountered on the North-West frontier of India, Northern Africa, Belgian Congo (Pergher and Casier), in Cochin China (Lépine) as well as in Central China, South China, Korea and Manchuria. There are also records from Sumatra, the Philippine Islands, N.E. Australia and Northern Gold Coast. It is common also in Japan, Mexico and Abyssinia, and was formerly frequent in Ireland and England.

In 1942 there was a limited epidemic, the first for many years, in Galway, W. Ireland. Serological tests indicated that it belonged to the epidemic serological type (Stuart-Harris and others).

In 1932 there was a big outbreak in Uganda, especially in districts of over 5,000 feet altitude. Similar occurrences have been reported in the Himalayas and Afghanistan.

There was a new wave in 1933 in Egypt and Chile, in 1934 in South Africa, in the Soviet Union, Rumania, Poland, Yugoslavia, Portugal and Hawaii. There has been no epidemic of importance in the United States of America in recent years. Typhus is most frequent in winter and spring months when heavy clothing affords an opportunity for lice-breeding.

Ætiology.—*Rickettsia prowazeki*, the specific virus, is conveyed by the louse (*Pediculus humanus*, var. *corporis* and *capitis*) ; in the blood it is filtrable and infective for monkeys and guinea-pigs as the rickettsiæ are present in the blood-plasma, especially in the blood-platelets, during the first five days. A developmental cycle of the rickettsia takes place in the intestinal tract of the louse (*see* p. 221). Infection is conveyed through the louse fæces, which are inoculated by scratching. Löffler and Mooser (1942) showed that head-lice play an important part in transmission.

Typhus blood was found infective for guinea-pigs and monkeys by Ricketts, Nicolle and Anderson ; later Wolbach, Todd, Palfrey and Pinkerton (1920-22) found intercellular *R. prowazeki* in lice in Poland. Nicolle, Conte and Conseil proved by experiment that the chimpanzee can be infected by lice.

So many physicians died of typhus during the 1914-1918 war and so many contracted the disease that other methods of transmission than by lice were suggested and it is probable (as accepted in the present conflict) that the virus may also be conveyed by droplet infection. There are German reports that infection has been acquired by medical men while taking blood for the Weil-Felix reaction. Typhus has also been conveyed by blood transfusion when the donor happened to be in the incubation period of the disease.

Pathology.—The rash is usually visible after death. There are hæmorrhages of the conjunctiva and, usually, areas of skin necrosis and gangrene. The blood is particularly dark and does not clot. The kidneys and liver show cloudy swelling. The spleen is usually moderately enlarged, with hyperplasia of the lymph follicles ; the substance is soft and diffluent. Bronchial catarrh is usually present, with hypostatic pulmonary congestion.

The eruption is due to proliferation of the endothelium and localized necrosis of the walls of the smaller blood vessels, with local collections of lymphocytes and plasma cells in the adventitia. These are the " typhus nodules " which resemble miliary tubercles, and were first described by Frænkel and subsequently by Aschoff, Wolbach and others. They are characteristic, and are found in the vessels of the skin, myocardium, brain and viscera (Fig. 41). The essential lesion is due to phagocytosis by cells of the vascular endothelium, followed by necrosis of cells which enclose rickettsiæ and their toxins. Lesions in the brain, resembling miliary

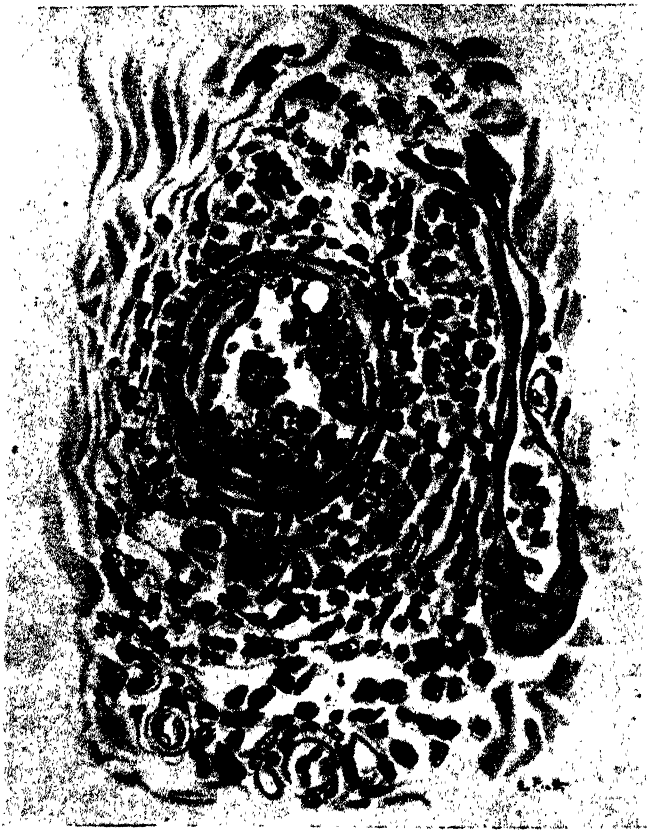
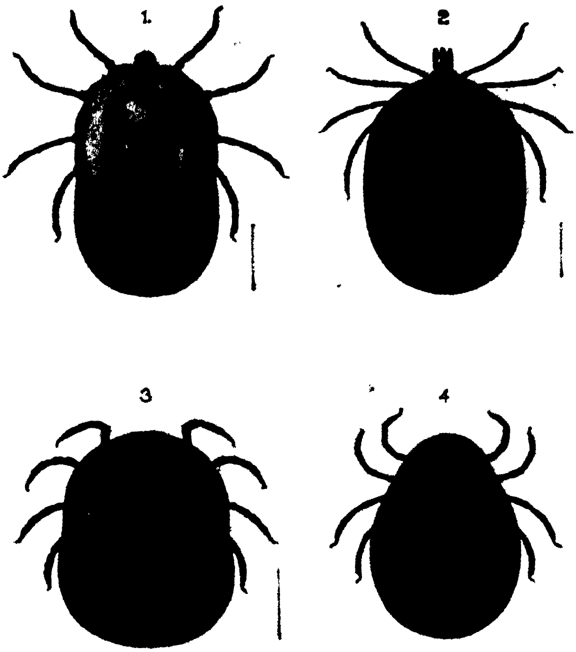


Fig. 41.—Typhus nodule. Section of arteriole of skin showing attached mural thrombus, composed almost wholly of phagocytic endothelial cells, with early proliferative perivascular reaction.

(*After Wolbach and Todd*)



1, *Margaropus (Boophilus) annulatus* (partially distended). 2, *Ixodes reduvius* (partially distended). 3, *Ornithodorus moubata*. 4, *Argas persicus*.

FEMALE TICKS.

PLATE VI

1

1 a

3

1.—Rash of trypanosomiasis. (*T. gambiense.*) (*Dr. I*

1(a).—Primary lesion, site of infecting tsetse bite on

2.—Dengue rash (*after Cleland, Bradley and MacDonald.*)

tubercles, are found especially in the basal ganglia, medulla and cerebral cortex.

The red marrow becomes hyperplastic and is converted into yellow marrow, though there is little increase in the myeloid elements.

Symptoms.—It has been said that the more clinicians see of typhus the more varied becomes the clinical picture.

The *incubation period* varies between five and twenty-three days, the average being twelve. The period of onset lasts about two days, during which the patient has rigors, headaches, pains in back and limbs, nausea and giddiness. Vomiting is frequent. Occasionally, fulminant cases (*typhus siderans*), with general convulsions and delirium, are met. On the third day the temperature rises suddenly to 103° or 104° F., and the face becomes congested, with general suffusion of the eyes. The headache is very severe (German—*Kopfwehkrankheit*) and with it goes a peculiar stuporose, drunken look not seen in any other disease except, perhaps, plague. The patient is drowsy, often delirious, usually with insomnia (Chart 12).

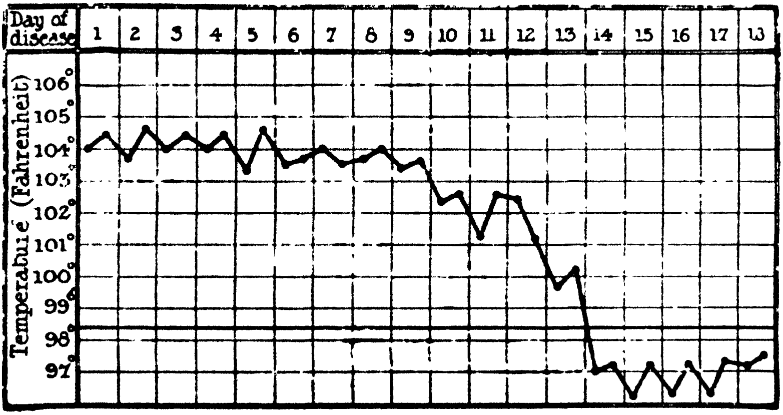


Chart 12.—Typhus Fever.

The mouth is foul, the tongue coated with a dense brown fur, the breath offensive. Epistaxis is frequent in the early stages and vomiting may be distressing. For twelve to fourteen days the temperature remains raised with slight, sometimes scarcely perceptible, morning remissions. The urine is concentrated, offensive, with a cloud of albumin, and urea and chlorides initially increased in amount. In severe cases there is often hæmaturia. The spleen is usually enlarged and palpable. German observers lay great stress on the changes in the cardio-vascular system, especially the low systolic and diastolic blood pressure.

The *rash*, so characteristic of typhus, may appear as early as the third day, but more usually on the fifth or sixth, upon the abdomen, inner aspect of the arms, spreading over the chest, back and trunk, usually pleomorphic, and only involving the face in severe cases. It may be absent in about 10 per cent. The term " mulberry rash " is usually employed to describe it, but it essentially consists of roseolar macules, with fine, irregular dusky mottling underlying the epidermis, best described in the words of Murchison as "*subcuticular mottling.*" Usually it becomes petechial and may then be seen especially on the hands and soles of the feet (Fig. 42).

Rarely, it is bright red, instead of a mingling of copper and purple ; sometimes, too, it may be hæmorrhagic. Papular spots are commonly encountered and may be circular or indefinite, but when petechial they may closely resemble flea bites. The rash fades very slowly and may remain visible for ten days. A fine brawny desquamation towards the end of the third week has been described ; it sometimes occurs on the soles of the feet.

Fig. 42.—Typhus rash in second week, showing typical distribution. The dark coloured areas are petechial ; the lighter coloured, less discrete areas disappear on pressure. (*After Wolbach and Todd.*)

In dark-skinned natives the typhus rash is necessarily very difficult to discern. To make the subcuticular mottling visible, a thorough cleansing of the skin and a good light are necessary. Congestion of the upper arms by a tourniquet, such as the band of a blood-pressure apparatus, usually renders the petechiæ more easily visible. This method has also been practised with success in the early diagnosis of the typhus rash in Europeans. In natives the rash is usually more pronounced around the umbilicus.

On the appearance of the rash there are usually signs of bronchitis and in severe cases often icterus; prostration and cardiac weakness become more pronounced; and with increase of the mental lethargy the patient sinks into the "typhus state." The expression becomes dull and vacant, the face flushed, with a peculiar earthy hue (*facies typhosa*). Cerebration is slow; the hands and tongue become tremulous and the patient becomes more difficult to nurse. The skin at this stage sometimes emits an odour which has been compared to that of "gun-washings," or that emanating from a cupboard containing well-blackened boots.

During the second week a low muttering delirium usually supervenes. Meningism is not uncommon. The secretion of urine may then be diminished or even suppressed. Often symptoms of cortical irritation, such as muscular twitchings, and incontinence of urine and fæces may be observed. The cerebro-spinal fluid is under pressure and there is usually an increase in the cell content. The patient is generally deaf.

In severe cases the pupils become pinpoint and the eyes "ferrety." As the fourteenth day approaches, signs of improvement may set in and the temperature falls by crisis, or sometimes by rapid lysis. Death generally occurs on the twelfth or fourteenth day, or it may be later, when the temperature is subnormal, from exhaustion or cardiac failure. The blood picture usually shows nothing very definite, but a moderate leucocytosis of 12,000 to 15,000 per c.mm., mostly large mononuclear cells, is usual. The blood is concentrated so that the hæmoglobin and red blood count are abnormally high.

Amongst native populations terrible complications due to sepsis and neglect may ensue. Terminal bronchopneumonia is common. The patients become extremely emaciated. Implication of the central nervous system is frequent, such as ataxia, violent tremors, mania or dementia. Hemiplegia or paresis of the limbs due to typhus nodules in the brain has been reported. Parotitis and noma are frequent. Abortion in pregnant women is common. Constipation rather than diarrhœa is the rule. The mouth becomes very foul, with the lips and teeth covered with sordes. Bedsores are frequent. Thrombosis of the femoral vein is not uncommon, while gangrene of the extremities, especially of the toes, due to arterial thrombosis, is frequently seen in wartime epidemics. One of the most distressing features is gangrene of the lung as a termination of typhus broncho-pneumonia. Mental symptoms are among the most important sequelæ. Recently it has been suggested that juvenile thrombo-angiitis obliterans (Bürgher's disease) may be due to antecedent typhus.

Relapsing fever and typhus frequently co-exist and this superadded infection is serious. Mild forms of typhus, lasting some ten days, are frequently seen in children, but it is usually the very young and the aged who most readily succumb. Aberrant forms of typhus fever without a rash may be encountered towards the end of an outbreak when immunity is high.

Convalescence is usually slow and prolonged, and during this period great care should be taken not to excite the heart. Snapper pointed out that thrombocytopenia is not infrequent in typhus and some cases, even after the typhus infection is over, show a typical anaphylactoid and sometimes even a thrombocytopenic purpura. Loss of hair on the head and legs is said to be common.

Most deaths occur between the eleventh and seventeenth days; the former date is said to be specially critical. The case mortality is negligible in children. It is 10–15 per cent. up to the age of forty, but 50 per cent. at fifty; over that age few survive. Relapses of typhus have been recorded. It appears that epidemic typhus has become so solidly established in man that some individuals, who have recovered from the first attack, retain the virus in their bodies and may develop a second, many years after the first, at a time when the bodily resistance is depressed.

Immunity.—On recovery from an attack of typhus the immunity is complete for a considerable time, but this gradually wears off. Apparent or mild attacks in persons with partial immunity are believed to constitute an important source of infection.

Diagnosis.—Conditions which may simulate typhus are readily differentiated by laboratory methods. As has already been noted, the rashes of other members of the typhus group closely simulate that of exanthematic typhus and can be distinguished with difficulty. Stress is laid on the rarity of rash on the face and the fact that it does not come out in crops. The "tongue sign", first described by Okuniewski, is said to be very helpful in bed-side diagnosis. The patient is unable to protrude the tongue when ordered to do so; this is attributed to perivascular infiltration in the region of the nucleus of the hypoglossal nerve.

The *Weil-Felix* reaction in high dilution is diagnostic, but false positive reactions may occur in infective hepatitis, enteric, trench and undulant fevers. The titre of agglutination rapidly rises to 1 in 500 towards the end of the fever. During convalescence it remains about 1 in 56–1 in 100 for weeks and even months. A reliable strain of *Proteus OX*19, as from the Oxford Standards Laboratory, should be employed.

In the course of the present war the Germans have produced a rapid method of diagnosis in ampoules of dried *Proteus OX*19, each containing enough for twenty tests. The contents are thoroughly mixed with vigorous shaking in 2 c.c. sterile salt solution to which sodium citrate has been added to prevent clotting. A drop of blood is placed on a glass slide and when a similar quantity of the diagnostic suspension is mingled with it agglutination is seen.

Dried blood in thick drops on a slide has been employed in the field. Three drops run together should form a round smear about 1 cm. in diameter. Emulsion is then made by rubbing up with a blue-stained suspension of Proteus *OX*19 or what is known as the "Tr. B.A. test." In positive reactions the bacteria form clumps and blood corpuscles run together. Immediate clumping is equivalent to the customary Weil-Felix reaction in a titre of 1 in 3200 or over. (Killed *Proteus OX*19 in suspensions to which alcohol has been added keep for several months.) Anamnestic reactions to *Proteus OX*19 result from previous attacks of typhus. When these can be excluded, Weil-Felix titres of 1 in 200 are diagnostic and a titre of 1 in 100 suggestive. Repeated tests are the best means of excluding fallacies. The frequent co-agglutination of typhoid bacilli by sera of persons who give a positive Weil-Felix reaction is due to anamnestic increase in agglutinins owing to previous infections.

Agglutination with suspensions of rickettsiæ grown on yolk-sac embryo is now being tried out in America. Probably by this method response appears earlier than in the Weil-Felix test and may be more reliable.

A pseudo-positive Wassermann reaction is frequently given by the blood before the crisis. On the same lines is the recently devised complement-fixation reaction of Bengtson and Topping, but this probably becomes positive later in the disease than the Weil-Felix.

The virus may be isolated from the blood at the height of the fever by inoculating 2–5 c.c. intraperitoneally into guinea-pigs and subsequently demonstrating rickettsiæ in the tunica vaginalis. Gear and Davis recently showed that South African gerbilles (*Tatera brantsi* and *T. afra*) are specially susceptible to typhus and die with heavy infection of the peritoneum. Exposure of these animals to X-rays definitely lowers their resistance.

Skin biopsy for the identification of the rash has been proved particularly useful. Sections show the typical lesions resembling periarteritis nodosa. The petechiæ on the skin are due to thrombosis of the smaller vessels.

An intradermal test was introduced by Giroud (1938). The patient's serum is mixed with a definite quantity of rickettsiæ (emulsion of the tunica of a guinea-pig infected with the murine strain). The emulsion is injected into the skin on the inner surface of the thigh of a rabbit. Normal serum is used as a control. If the patient has, or has had, typhus no reaction appears, but in the controls it is marked.

Differential diagnosis.—This has chiefly to be made from typhoid and is based upon the onset and course of the temperature curve and in the character of skin eruption. In typhus the temperature climbs quickly to a high level where it remains, in place of the slower escalator rise of typhoid fever. There is, moreover, a mild leucopenia in typhoid ; a mild leucocytosis in typhus. The diffuse roseolar rash of paratyphoid (especially paratyphoid A) may sometimes resemble that of typhus, but nervous signs and symptoms are less severe, and roseola of palms of hands and soles of feet is not found in typhoid as in typhus.

The differential diagnosis from *septic meningitis* with skin eruptions may be difficult, and determinable only by examination of the cerebrospinal fluid and by the Weil-Felix reaction. Differential diagnosis has also to be made from measles, especially the malignant form commonly observed in native races. In this case Koplik's spots are of assistance ; moreover, in measles the rash is brighter, its edges are definitely more marked and it is more profuse on the face. In the tropics, dengue, especially in the initial stages, may prove difficult, but the patient is never so ill, nor is suffusion of the face so marked. In severe smallpox the initial scarlatiniform rash may be confusing, but characteristic smallpox lesions are seen first on the face. Cerebro-spinal fever, purpura and relapsing fever have to be considered ; the latter is frequently found in combination with typhus.

Treatment.—Up to the present no specific drug treatment of typhus has been introduced. Therefore special attention must be paid to details of nursing and to the hygiene of the mouth. The recumbent position is essential, and every precaution should be taken against bedsores. It is important that the patient should have as much fresh air as possible. It is customary to give stimulants, the most favoured being port wine—about eight ounces in twenty-four hours being sufficient.

Cardiac stimulants are indicated, such as tincture of digitalis, digitalin (gr. $\frac{1}{10}$) or digitoxin (digitaline crystallisée gr. 1/100). Strychnine, gr. $\frac{1}{50}$ is also a good stimulant. Lumbar puncture should be employed to relieve delirium and other cerebral symptoms, for, as a rule, the cerebrospinal fluid is under pressure. Plenty of fluids should be given and the diet should be as nutritious and easily digestible as possible.

Hopes were entertained at one time that convalescent human typhus serum, injected in suitable amounts, might modify the disease. The results have not been encouraging. In Tunis, benefit has been claimed from injection of serum from a horse[1] immunized with living rickettsiæ from infected mouse lung, but it is clear that none of the sera hitherto employed contain antibodies corresponding to the heat-labile and heat-stable rickettsial antigens (Felix). Felix is at present experimenting with serum from animals inoculated with *Proteus*.

For toxæmia, injections of subcutaneous saline or glucose solution with twenty to forty drops of 1 in 1000 adrenalin, up to a total of 500–1000 c.c. daily, support the patient and relieve dryness of the throat and lips. For hyperpyrexia tepid baths are indicated. Chloral hydrate in doses of half to one drachm is the best drug for relieving headache and insomnia. During convalescence preparations of iron, arsenic, and glycerophosphates are employed.

Italian workers have suggested that vitamin C has an influence on the hæmorrhagic symptoms of the disease, and inject ascorbic acid (0·25 grm.) intravenously three or four times daily. Sulphonamides, especially sulphapyridine, have been used recently in the treatment of typhus in Warsaw, especially for its complications, of which the most dangerous is pneumonia, due to secondary pneumococcal infection. The general impression has been favourable in so far as these drugs tend to prevent pneumonia. There is, however, no evidence that they influence the typhus infection itself.

Scheller, in the treatment of typhus in the present war, has used *chinifortan*, a combination of quinine and sulphonamide, 2 c.c. twice daily intravenously with 2 tablets by the mouth, continued to the end of the fever. The total daily dose is 1·05 grm. of quinine and 2·1 grm. of sulphonamide. Atebrin (mepacrine hydrochloride) followed by plasmoquine has been given, purely empirically, by the Germans (Van Meerendonk, 1942) in Russia during the present war. The duration of fever is said to be reduced by several days and the general course of the attack becomes less severe. Where no striking response is obtained there is nearly always complicating bronchopneumonia.

Prophylaxis.—The quarantine period of typhus is fifteen days. The main prophylactic measures consist almost exclusively in the destruction of lice. The body should be shaved, including the pubes and axillæ, the hair of the head cropped and a cresol bath taken. The underclothing should be smeared with a preparation of naphthalene and soft soap and, whenever possible, all clothing, including blankets and bed clothes, should be disinfected by heat. Buxton states that lice and eggs are killed in 45 minutes at 50° C., and in 5 minutes at 54° C. It is essential to make sure that all parts of the garments are subjected to heat, and this is especially important when steam is used. Steam admitted to the bottom of a chamber and escaping from the top may follow certain paths only and leave parts of the clothing untreated. It is wise therefore to admit steam to the top of the chamber and force it to escape from the bottom ; it then permeates to all parts. Busvine proved that spraying clothes with lethane 384 is effective. The liquid is applied by a hand sprayer and 2–4 c.c. is enough for each garment. Lethane must not come into direct contact with the skin. Disinfestation of clothes on a large scale is carried out on railway luggage vans by closing the doors and turning on superheated steam from the engine. Soaking clothes for several hours in 2 per cent. lysol, or dettol, destroys the pediculi and their eggs.

---

[1] Wolman in Abyssinia (1944) reported favourably on an anti-typhus serum prepared by injecting horses with living rickettsiæ from lice intestine. The dose is 20 c.c. subcutaneously, twice on the first day and once on three succeeding days, up to 100 c.c. The mortality of the treated group was 3·6 per cent., compared with 10·9 per cent. in controls.

A potent insecticidal powder (A.L.63) for use in clothing has recently been prepared, and, when applied to body belts, has proved very effective in the present war. A great advance has been made by the use of the insecticide dichlordiphenyl trichlorethane (D.D.T.), which is the active ingredient of the U.S. Army louse powder.[1] It was first synthesized in 1874 and covered by patents taken out in Britain by the Swiss firm of Geigy A.G. In powder form it is diluted with an inert dust, bentonite, and can be made up in emulsion for spraying. It is lethal to all insects, including lice and bugs, and remains effective in clothing after frequent washings. This seems a really important discovery. It is quite harmless to man.

Prophylactic inoculation.—Several methods of active immunization against louse-borne typhus are in use in various parts of the world (*see* p. 250).

II. MURINE TYPHUS—FLEA TYPHUS

Synonyms. Endemic typhus—Brill's Disease.

Geographical distribution and epidemiology.—This is worldwide, especially in Mexico, North America and Palestine. Typhus-infected rats have been found in the Mediterranean basin, Syria, Greece, Toulon and North Africa. The seasonal incidence remains constant ; the majority of cases occur in summer and autumn. The incidence is twice as high in males as in females and the negro is less susceptible than the European. In West Africa this form has been found not uncommonly where it had not previously been suspected.

History.—Described originally in 1898 by Brill amongst the Jewish population of New York, this was originally regarded as a particularly mild or larval form of exanthematic typhus. The infection was brought by immigrants from the typhus regions of South-Eastern Europe, so that 90 per cent. of cases occurred in foreign-born peoples. It soon became apparent that it was sporadic, not carried by lice or spread in the manner peculiar to louse-borne typhus.

---

[1] D.D.T is a white crystalline powder, insoluble in water, remarkably soluble in paraffin and fairly soluble in vegetable oils. Is stable to sunlight and practically non-volatile. It should not be inhaled, gloves must be worn and precautions taken to avoid spraying food. Delousing is best effected by spraying up the trousers and sleeves, down the neck and round the waist. Its value in combating typhus was demonstrated in the Naples outbreak in 1944.

Ætiology.—Nicolle in Tunis and Zinsser in America took the view that murine typhus is the more primitive disease. It is clear that it is not spread from man to man, but from rat to man, the brown rat, *Rattus norvegicus*, being mainly concerned. They think that the infection may overflow to man, generally producing isolated cases without further man-to-man spread. According to an evolutionary point of view, this infection has undergone two mutations, by changing both its vertebrate and invertebrate host. In Mexico a type of typhus exists in rodents and man which may be regarded as intermediate between the murine and exanthematic types. It is also true that many species of rickettsia are unstable. The more recent origin of epidemic typhus is indicated by the fact that *R. prowazeki* var. *mooseri* is harmless to the flea, while *R. prowazeki* causes death of the louse, to which it may be regarded as less adapted. It therefore appears probable that the endemic form may be easily converted into the epidemic, and that typhus infection may be maintained in the inter-epidemic period by rats. Thus, Raynal, Fournier and Velliot (1939) have adduced evidence in Shanghai that, under certain conditions, the rat virus can be converted from the rat-flea-rat cycle into the man-louse-man cycle.

On epidemiological grounds the association of endemic typhus with rats and grain stores was first suggested by Hone (1922) in Australia and subsequently by Maxcy (1926) in America; in 1931 proof was provided by Mooser, Dyer and his colleagues that the rat was the reservoir, and that rat fleas (*Xenopsylla cheopis* and *X. astia*) were carriers of the virus. Under normal conditions the infection is spread from rat to rat by the rat-louse (*Polyplax spinulosa*). Rats (*R. norvegicus*) collected from areas where numerous cases of endemic typhus had occurred, were chloroformed, then fleas collected, emulsified and injected intraperitoneally into guinea-pigs. After four days' incubation period these reacted with fever and swelling of the testes (Neill-Mooser reaction).

In the same year Mooser, Castañeda and Zinsser in Mexico demonstrated endemic typhus virus by injecting guinea-pigs with a brain emulsion of rats caught in the endemic area. Dyer and his colleagues then demonstrated that *X. cheopis* became infected when fed upon infected rats and could convey typhus to other rats.

Zinsser subsequently showed that the exanthematic, or human, virus and the rat virus are two varieties of the same species, resembling each other in their antigenic properties, but *not* identical. Neither he nor Mooser could *permanently* transform the human virus into the rat virus. Thus, Zinsser and Castañeda found that formalin-killed murine typhus rickettsiæ conferred a higher degree of immunity against a homologous virus than against exanthematic typhus

General considerations.—It may well be asked why does not endemic typhus spread like plague, considering the close connection between rat and man? The answer is partly that *X. cheopis* in endemic typhus is not nearly so heavily infected as fleas in plague or as lice in epidemic typhus. The difference in the vectors of exanthematic and endemic typhus also accounts for the fact that exanthematic typhus is a disease of the winter months and of crowded insanitary peoples, whereas endemic typhus is a disease of warm weather, not associated with crowded humanity, but with the presence of rats. Other forms of typhus resembling Brill's disease have been described from Australia, North and South Africa, whilst ship-fever of Toulon (*fièvre nautique*) is a local form ; other varieties may be those forms of trench fever with a rash, and also the urban (W) form of tropical typhus described by Fletcher and his colleagues in Malaya with a tendency to spread amongst those engaged in handling grain.

Zinsser (1934) and Plotz (1943) think that the disease described by Brill is recrudescence or relapse of epidemic typhus, but that endemic typhus in the South United States and Mexico is *murine typhus*. In the former the reservoir of the virus is man. These views have received support from the new complement-fixation technique with rickettsial antigens.

Symptoms.—The symptoms resemble those of exanthematic typhus, but are much milder in every respect. The mortality rate is very small (about 1·5 per cent).

Diagnosis, differential diagnosis and treatment are identical, but Bengston and Topping in America showed that the agglutination test with rickettsial suspensions should clearly differentiate between murine typhus and Rocky Mountain fever.

III. TRENCH FEVER (FIVE-DAY FEVER, VOLHYNIAN FEVER)

Definition.—This curious fever played a prominent part in the medical history of the 1914–1918 war on the Western (French) front, especially amongst the troops and to a lesser extent amongst civilians. It also occurred in Poland, Russia, Northern Italy and Macedonia. Until the present war it was not encountered after 1918 under natural conditions, though a fever resembling it appeared amongst laboratory workers in Weigl's laboratory, who had been feeding lice on their bodies (Herzig, 1939). The Germans have recently reported it on the Russian front.

Its association with rickettsiæ and its transmission through the louse are claims for its inclusion within the typhus group. Trench fever is characterized by an initial febrile period, a tendency to relapse, periodic pyrexia and hyperæsthesia of the shins.

Geographical distribution.—Possibly it may be identical with "Volhynian fever," known to Polish physicians for some years before 1914. It was first recognized as a specific entity during 1915, when it appeared in all the European theatres of war, and no less than 800,000 cases were recognized in the Allied Forces in France, with isolated instances notified from Italy, Greece, Egypt, Iraq and Russia.

Epidemiology.—Trench fever is transmitted by lice alone, and the blood of the patient remains infective to these insects for long periods. These factors suggest that the disease might have a wider distribution than was at first suspected, but this has not been borne out. Trench fever cases have a group distribution consistent with the migrating habits of the louse, which tends to leave the fevered human host.

Ætiology and transmission.—*Rickettsia quintana* is transmitted in the excreta of the louse and multiplies in the cuticular margin of the epithelium of the midgut of that insect (p. 221). The virus exists in the blood of man and can be transmitted by inoculation of blood, or plasma.

It has also been found in urine, sometimes in saliva, but never in fæces. It is killed in one hour at 70° C.

The infection is conveyed by lice fed on trench fever patients, the infected excreta being inoculated by scarification; lice crushed and rubbed into the scarified skin also convey the disease. A cycle of development of rickettsiæ takes place in the louse and occupies five days, during which time the insect is not infectious. Lice remain infective for at least twenty-five days; the virus is not hereditarily transmitted through the louse. The infection persists for a long time in the blood of the patient and can be conveyed eleven weeks after an attack. Neither high nor low temperatures appear to influence the developmental cycle of this rickettsia in the louse.

Symptoms.—Several types of fever were originally described, but relapsing pyrexia is usually present. Paroxysms of fever, lasting one to two days, recur at intervals of four to six days. An undulating type, with waves of recurring periodicity of four to ten days, has also been described. The incubation period is about two to three weeks; by scarification eight days; by transference of lice fourteen to thirty-eight days. The onset is usually sudden. There are headache, giddiness, pains in back and legs, often profuse sweats, flushing of face and injection of conjunctivæ. The spleen is enlarged in one-third of cases. There is no marked exanthem, as in typhus, but a pale pink erythematous or roseolar eruption which disappears on pressure has been described in one-third of the cases, usually coinciding with a relapse.

Tenderness and pains in the shins are characteristic and often very acute indeed, but usually not present in the early stages. Severe pains are also felt in knees and thighs, sometimes in the gastrocnemii. There is nothing characteristic in the blood, save a moderate leucocytosis of 10,000–14,000 per c.mm. Sequelæ are few and mild, such as slight febrile attacks, myalgia, tachycardia and debility.

The disease is never fatal, but shin pains often persist after subsidence of other symptoms. Complete recovery is the rule.

Treatment.—The patient should be confined to bed for at least three weeks. Pyramidon, 1–2 grm. daily, is the only drug which has been found to have any effect upon the pyrexia or shin pains. Omnadin, a mixture of albuminous bodies, is recommended for relief of pain.

IV. MITE TYPHUS.—TSUTSUGAMUSHI

Synonyms. Tropical typhus; Shimamushi; Japanese river fever; Kedani mite disease; Scrub typhus, "K form."

Definition.—A typhus disease with a high case-mortality rate, characterized by the presence on the skin of an *initial eschar*, supervening on the bite of a species of microtrombidium (the larval stage of *Trombicula*—a "velvet mite"). This is followed by an ulcer, lymphangitis, and a typhus-like rash.

History.—Ancient records indicate that it has been known in Japan for over a thousand years, but the disease was first accurately described by Palm (1878) and subsequently by Baelz and Kawakami. Hatori (1919) gave a full account of the epidemiology, whilst Hayashi first described in the endothelial cells minute intracellular bodies which are now recognized as rickettsiæ.

In 1925 Fletcher separated this disease in Malaya from murine typhus. The latter was known as the "urban type," the former as "scrub typhus." Subsequently, it became possible to separate these two types of typhus serologically.

Geographical distribution and epidemiology.—Formerly considered to be confined to the banks of two rivers on the west of the island of Nippon, Japan—the Shinanogawa and the Omonagawa, one of its tributaries—the disease is now known to have a much wider range.[1] It becomes epidemic after the flooding of these rivers, when hemp is raised on the inundated land, and appears in the harvesters during July and August. Tsutsugamushi occurs also in Korea, in Formosa (in the highlands as well as on the coastal plains), in Malaya, Sumatra, Borneo, Indo-China and Northern Queensland (where it was known as "Mossman fever"). Isolated cases have been reported from Ceylon, New Guinea, the Pescadores, Burma and India (Simla Hills, Madras and Bombay). In Malaya, tsutsugamushi is a place disease and the infection clings to the rank vegetation of oil-palm plantations and coarse grass which is used as cattle fodder.

Ætiology.—The organism of tsutsugamushi or "scrub typhus" is known as *Rickettsia orientalis*. This organism is conveyed by the bite of an acarus (locally known as *akamushi*—the red insect), which is the larva of a "velvet mite," *Trombicula akamushi* (0·9 mm. in length). The adult stage is non-parasitic. This larva is popularly known as the kedani mite or "patau" (Figs. 319, 320, p. 945) and the Japanese have always regarded it as the vector of this fever. (This mite somewhat resembles the harvest mite—the larva of *T. autumnalis*—and was formerly and incorrectly known as *Microtrombidium* or *Leptotrombicula akamushi*). In Sumatra and Malaya, however, the vectors are larvæ of *Trombicula deliensis* and *T. schüffneri* respectively, which infest the undergrowth and long grass ("lalang") in clearings of the forest and there they are probably distributed by the crow pheasant (*Centropus bengalensis javanicus*). *T. deliensis* is pale ochre, *T. akamushi* bright vermilion. It is probable, though not absolutely proved, that wild rats (*R. rattus diardi*), the rural rat (*R. rattus jalorensis*) and the house rat (*R. concolor*) act as reservoirs of infection (Lewthwaite and Savoor, 1937). The larval trombicula occurs numerously on the ears of the field vole (*Microtus montebelloi*) and other rodents—*Mus jerdoni*, *R. rattus rufescens*, *R. decumanus* and *R. agraicus*. In Korea and Formosa it is disseminated by a small warbler (*Acrocephalus stentorius orientalis*), domestic fowls, the pheasant (*Phasianus colchicus formosanus*) and a quail (*Turnix javanica atrigularis*). In the Mandated Territory of New Guinea, Gunther (1939) regarded *T. minor* as the probable vector, its principal hosts being the rat or bandicoot (*Echymipera cockerelli*), bush pig, fowl, turkey, cassuary and ground pigeon. In Papua the vector is probably *T. hirsti*.

The rickettsiæ have been found in the body-cavity of the adult mite, *Trombicula akamushi*, and in the salivary glands of the infective larval stage, and are now known to persist from one generation to the next—about 30 days. The infection may originally be contracted by the adult trombicula and thereby may be transmitted to the larva. The larval *Trombicula* requires one single meal of blood to complete its development. It attaches itself to vegetation, such as lalang grass or scrub, along the course of rivers. (*R. orientalis* remain viable in lice for about seven days, but cannot be conveyed, but in the flea, *X. cheopis*, it persists for eleven days so that the infection can be transmitted, under experimental conditions, by this ectoparasite.)

---

[1] It is officially stated to be endemic in the Niigata, Yama and Akita provinces, and in the districts of certain rivers—the Uonuma, Shinano and Aka rivers.

R. orientalis occurs in the blood in the incubation period of the disease. Monkeys can be easily infected with as small a quantity as 0·001 c.c. The organisms are destroyed by heating at 55° C. for ten minutes.

Anigstein's claims to have cultivated the organism in broth have not been substantiated, but it may be maintained on yolk-sac embryo as described on p. 223, as well as in tissue culture made from the endothelium of Descemet's membrane of the eye with additions of normal aqueous humour and rabbit plasma.

Nagayo and others succeeded in transmitting the rickettsiæ by intraocular inoculation in guinea-pigs, also by intratesticular injection in rabbits, in which they produce a characteristic reaction. Cross immunity experiments have shown that no immunity exists between *R. orientalis* and *R. prowazeki* and that therefore these two members of the typhus group are distinct (*see also* p. 224).

Pathology.—The lesion at the site of the infective mite bite undergoes coagulation necrosis and affects the epidermis, corium and surrounding tissues and is well delineated by a boundary line. This forms the *eschar* or ulcer, which is usually though not invariably present. The spleen is enlarged, with tense capsule, soft and friable pulp, and focal necrosis; similar lesions are found in the enlarged and congested liver. The lungs are congested, and hypostatic bronchopneumonia is frequent. There is a general lymphadenitis; glands in the vicinity of the initial lesion are specially affected and may show central necrotic lesions.

Kouwenaar found that histologically the " typhus nodules " differ from those of the exanthematic form in that the chief change takes place in the perivascular infiltration and that the intima of the blood vessels is secondarily involved.

Symptoms.—The person attacked by the mite does not usually notice the bite, but later feels a pricking sensation when he happens to touch the spot. The mite, or mites, can easily be seen through a strong magnifying glass, with their heads and bodies buried in the skin, but only when they are carriers of the disease do any definite pathological changes take place round the lesions they inflict. After an incubation period of from four to ten days, the disease usually begins with malaise, frontal and temporal headache, anorexia, chills alternating with flushes of heat, and prostration. Presently the patient becomes conscious of pain and tenderness in the lymphatic glands of the groin, armpit, or neck. On inspection of the skin of the corresponding lymphatic area there is sometimes discovered—usually about the genitals or armpits—a small (2 to 4 mm.), round, dark, tough, firmly adherent eschar surrounded by a painless livid red areola of superficial congestion. This is the initial ulcer. Sometimes it may be merely a papule which develops and disappears during the incubation period and therefore is seldom visible. Lewthwaite makes a point that an *ulcer* is not by any means invariable. Occasionally two or three such eschars are discovered. Although a line of tenderness may be traced from the sore to the swollen, hard, and sensitive glands, no well-defined cord of lymphangitis can be made out. The superficial lymphatic glands of the rest of the body, especially those on the side opposite to the glands primarily affected, are also, but more slightly, enlarged.

Fever of a more or less continued type now sets in, the thermometer mounting in the course of five or six days to 104° or 105° F. The conjunctivæ become injected ; the eyes are half-closed, watery and faintly glistening. Photophobia is invariable. At the same time, a considerable bronchitis gives rise to harassing cough. The pulse is full and strong, ranging rather low—80 to 100—for the degree of fever present. The spleen is moderately but distinctly enlarged, and there is marked constipation.

About the sixth or seventh day an eruption of large dark-red papules appears on the face, tending to become confluent on the cheeks, and fading on pressure. It extends to the forearms, legs, and trunk, being less pronounced on the upper arms, thighs, neck, and palate. Simultaneously, a minute lichenoid eruption breaks out on the forearms and trunk. This usually lasts from four to seven days ; if but slightly marked, it may fade in twenty-four hours, becoming pigmented.

During the height of the fever the patient is flushed, and at night may be delirious. He complains incessantly, probably on account of a general hyperæsthesia of skin and muscles. Deafness is also a feature.

As the disease advances, the symptoms become more urgent ; the conjunctivitis is intensified, the cough becomes incessant, the tongue dries, the lips crack and bleed, and there may be from time to time profuse perspiration. By the end of the second week—sooner or later according to the severity of the case—the fever begins to remit, the tongue to clean and, after a few days, temperature falls to normal and the patient speedily convalesces. There is a well-marked leucopenia. The red cells are normal, but there is a decrease in the coagulability of the blood. Bronchitis, diarrhœa, or diuresis may occur during the decline of the fever. The circular, sharp-edged, deep ulcer left after the separation of the primary eschar—usually during the second week—now begins to heal, and the enlargement of the glands gradually to subside. The urine is albuminous and gives the diazo-reaction.

Such is the course of a moderately severe case. In some instances, however, the constitutional disturbance is very slight, although the primary eschar may be well marked and perhaps extensive. On the other hand, the fever may be much more violent, and complications, such as parotitis, melæna, coma, mania, cardiac failure, or œdema of the lungs may end in death. Similarly, the duration of the disease varies according to severity from one to four weeks, three weeks being about the average. Relapses do not occur. It has been stated that many persons bitten by infected mites complain of headache, oppression, general malaise and numbness at the site of the bite. These may subside in two or three days and may be caused by the secretions of the mite, but not by *R. orientalis*.

This view has gained some support from the fact that such phenomena have been evoked by injecting an emulsion of freshly-macerated *T. akamushi*. Emulsions made with infected mites usually produce local necrosis.

Pregnant women contracting tsutsugamushi mostly abort and die.

According to Hatori, reinfection may occur.

The death-rate in Japan is high—from 25–30 per cent.—but much lower in Sumatra (0–15 per cent.).

Diagnosis.—The Weil-Felix reaction has proved of great value in diagnosis (*see* p. 230). The serum does not agglutinate cultures of *OX*19, or OX_2, but only *OXK* (Kingsbury strain) and this appears to be quite clear and definite. The main type of antigen is therefore *OXK*. Filtrates of *OXK* have been employed for an intradermal test (Kuroda). A positive reaction is said to supervene within a period of two hours, during the first few days of the illness only, but a negative reaction ensues after the sixth or seventh day.

United States medical authorities report that *R. orientalis* is easily isolated in the early stages by grinding up blood clot with normal saline and centrifuging at low speed; 0·3 c.c. of the supernatant fluid is inoculated intraperitoneally into mice. Death occurs 10–16 days later, and rickettsiæ are demonstrated in peritoneal smears.

The limited geographical distribution, together with the initial necrotic ulcer and lymphadenitis, suggest the diagnosis. Plague and tularæmia may possibly be considered, but even if primary vesicles or ulcers occur in these diseases, the matting together and exquisite tenderness of the lymphatic glands should be suggestive.

The differentiation of measles and dengue may also have to be considered.

Treatment.—The site of the bite should be treated by cauterization or extirpation.

Recently, stabilarsan, in two doses of 0·15 grm. and 0·3 grm. at four days' interval, has been employed with success. Lumbar puncture and drawing off fluid under pressure has had good results. The U.S. Army Medical Department has used penicillin in New Guinea, in maximal doses, with no effect. As hypochloræmia may develop, common salt, 6–8 grm., should be given daily.

Prophylaxis.—In a mite-infested country all parts of the body should be properly protected. For this purpose a mite-proof suit has been devised by Hayashi and Nagayo. All articles of clothing used in infected fields should be sterilized, and the parts of the body exposed to mite-bites bathed with Vleminckx's solution. The most effective measure is to burn down bushes and grass in the endemic area before bringing it under cultivation. *Dimethyl*, or *butyl, phthalate* sprayed on clothing and trousers has proved effective in warding off larval *Trombicula*.

For prophylactic inoculation, *see* p. 250.

V. TICK TYPHUS—ROCKY MOUNTAIN SPOTTED FEVER

Synonyms. Rocky Mountain Fever; Black Fever; Blue Disease.

Definition.—A specific fever supervening on the bite of ticks—*Dermacentor andersoni* and *D. variabilis*—and resembling, symptomatically, exanthematic typhus. Other species of tick have also been incriminated.

History.—For upwards of forty years a peculiar disease, variously named "spotted fever," "blue disease," "black fever," had been recognized as endemic in limited districts of Montana, Idaho, and Wyoming, America. Wolbach described in 1919 a rickettsia body as the germ-cause of the disease. In 1906 King ascertained that the disease supervened on the bite of *Dermacentor andersoni* (*D. venustus*)[1] (Figs. 322, 323, pp. 948, 949). On the eastern borders of its range the vector is *D. variabilis* (the common dog-tick of North America).

Geographical distribution and epidomiology.—First described in 1896, it was originally thought to be confined to several of the Western States of the American Union: Idaho, Montana (Bitterroot Valley), Wyoming, Utah, Nevada, Oregon, Colorado, New Mexico and Washington States. It is now known to be divisible into two varieties, eastern and western. On the whole, the latter is thought to be the more deadly. The eastern form is gradually spreading and has been reported from 32 States, as well as from E. British Columbia, Alberta and Saskatchewan, the only exceptions being Maine, New Hampshire, Vermont. Connecticut, Wisconsin, Rhode Island, Michigan and Kansas.

Principally found in valleys and near the foothills of the mountains, it occurs in sharply-defined and limited areas. A new South American focus in Colombia was originally discovered by Patiño-Camargo (1935) on the Tobia river, a tributary of the Rio Negro, in a narrow valley of the Magdalena basin at an altitude from 2,300 to 4,100 feet, and a second, somewhat to the north-west, on the Villeta at 1,650–4,300 feet. The high death rate (95 per cent.) and the susceptibility of laboratory animals to inoculation made it probable that the rickettsia is identical with *R. rickettsii*. The tick vectors appear to be *Amblyomma cajennense* and *Dermacentor nitens*. The possibility of the identity with the tick-typhus of São Paulo (Brazil) has also to be considered, and it is closely related to *Fièvre boutonneuse*. (Cf. evidence of Anigstein and Bader, *infra*.)

In the north-western regions of the United States the vector is *Dermacentor andersoni*, which is prevalent from the middle of March to the middle of June, and in that region the majority of cases occur in April, May and June, occasionally in July and September. In eastern States the vector is *D. variabilis*, which appears in March and December, and most of the cases are reported in June, July and August. The infection conveyed by these ticks is therefore more common in women and children because dogs bring ticks into the houses.

As a result of recent work it is becoming apparent that spotted fever is more widely distributed in America than was formerly considered probable, and that two principal types of the group in the Western Hemisphere can be distinguished—one transmitted by ticks of the genus *Dermacentor*, the other by *Amblyomma*; the latter covers the greater portion of Texas and a large part of South America.

Ætiology.—Originally known as *Dermacentroxenus rickettsi*, the organism has been renamed *Rickettsia rickettsii*. There is conclusive evidence that *R. rickettsii* is introduced by the bite of the tick; only the adult normally attacks man (*see* p. 949). Doctors are very susceptible, as is shown by the number of investigators who have perished from this infection. (In recent years Brumpt became accidentally infected in his Paris laboratory, but recovered.)

---

[1] The names *D. venustus* and *D. andersoni* refer to the same species. The differences in the of the tick used by various authors have resulted in a good deal of confusion. *occidentalis*, apparently distinct species, have at various times been incriminated as carriers of the infection. *D. variabilis* is the eastern representative.

The natural hosts of the wood tick, *D. andersoni*, are the Rocky Mountain goat, sheep, black bear, coyote, badger and lynx, but the larval stages develop principally on ground squirrels (*Citellus columbianus*) and the woodchuck (*Marmota flaviventris*). According to Bishopp and Smith, the immature stages of the dog tick (*D. variabilis*), are found on the meadow mouse (*Microtus pennsylvanicus*). The disease tends to occur in the spring months when these ticks abound. These facts naturally gave rise to the idea that the animals acted as reservoirs of the disease (*vide infra*).

The larva, nymph, adult male and female ticks have been proved efficient intermediaries for the parasite, whilst Dyer and others showed that the rickettsiæ are transmitted through the egg to the larva in a hereditary manner.

The proportion of infected ticks under natural conditions is quite small—only 1 in 296 in Rickett's experience. He originally suggested from differences in the case mortality (in Montana 90 per cent. : in Idaho 5 per cent.) that two species of tick were capable of transmitting infection—*D. andersoni* and *D. variabilis*—and the suggestion proved correct. After feeding on infected blood there is a period of invasion which lasts 12 days, during which a multiplication of rickettsiæ takes place and the virus is converted into "*tick* [illegible]

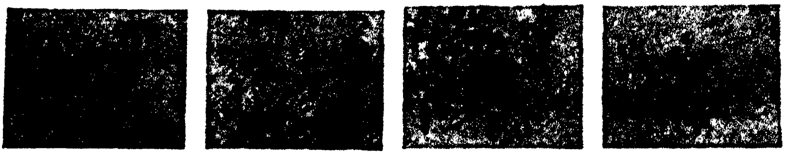


Fig. 43.—Microphotograph of *Rickettsia rickettsii*. × 2,000. (*Dr. A. C. Coles.*)

The original suggestion by Ricketts that the reservoir of the virus of this deadly disease was to be found in the ground squirrel, chipmunk and Rocky Mountain goat has not been confirmed. The recent work of Parker and colleagues, in Oklahoma, and of Anigstein and Bader in Texas (1948) affords grounds for believing that spotted fever intergrades between the South American form on the one hand and *Fièvre boutonneuse* on the other. In an outbreak in Oklahoma the typhus infection was transmitted by nymphs of *Amblyomma americanum*. In infected guinea-pigs the rickettsiæ are identical with *R. rickettsii*. The natural reservoir in this case was for the first time proved to be a rodent, the pocket gopher (*Geomys breviceps dutcheri*). In Texas, evidence pointed to the dog as the natural reservoir, and to the dog tick (*Rhipicephalus sanguineus*) as the vector, as well as *A. americanum* and probably also *A. maculatum*.

In human tissues Wolbach first observed minute bodies, staining with Giemsa, within the endothelium of blood vessels, in the substance of human and guinea-pig testes. The same forms were identified in the bodies, salivary glands and eggs of *Dermacentor*. Two morphological types were distinguished, one a lanceolate diplococcal form found in the circulating blood as well as in the endothelial cells and containing chromatin : the other rod-shaped and staining blue. (Fig. 48.)

Pathology.—In addition to the skin rash, there is usually bronchopneumonic consolidation or hypostatic congestion of the lungs, with subserous petechial hæmorrhages. Similar lesions are frequently seen in the brain. The myocardium is softened ; the spleen enlarged and firm ; the lymphatic glands generally enlarged ; focal necrosis of the hepatic cells and congestion of the renal cortex are found. Constant lesions, both in man and in artificially infected animals, are hæmorrhages into the genitalia and. quite often, gangrene of the prepuce and scrotum. Vascular nodules are a constant feature, but not so striking as in typhus, with perivascular mononuclear infiltration. Rickettsiæ are found in endothelial cells and in smooth muscle cells of the vessel walls.

Symptoms.—The incubation period is 3–7 days. The attack is ushered in by chills, which are repeated with diminishing severity at irregular intervals throughout the attack. By the second day the temperature rises to 103° or 104° F. and by the fifth to 105° or 107° F. A typhus condition supervenes, with intense headache, photophobia, irritability and meningeal irritation. If the patient is to recover, the temperature begins to fall at the end of the second week and the fever usually subsides by lysis. There are intense muscular pains and very often an agonizing arthritis.

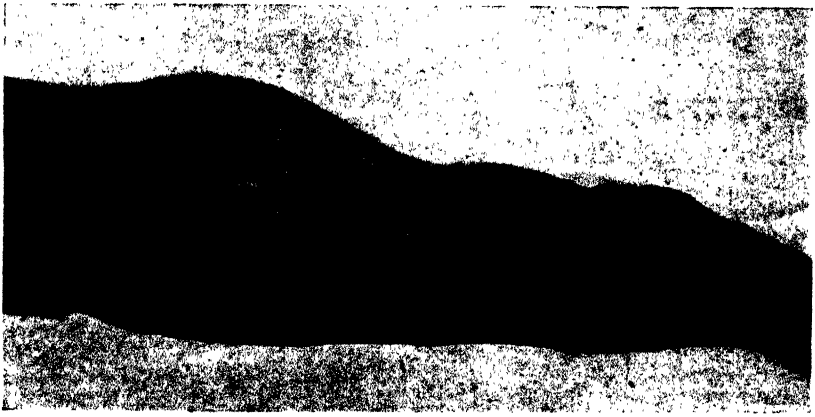


Fig. 44.—Rocky Mountain spotted fever on tenth day, showing confluent hæmorrhagic areas and a necrotic pressure area of the skin over the buttock. Texas outbreak conveyed by *Amblyomma americanum*. (*By courtesy of Dr. L. Anigstein.*)

The rash appears from the fourth to seventh day. It is first seen as small rose-coloured spots but soon becomes petechial, spreading so as to become confluent, especially on the more dependent parts. It is, on the whole, redder and more florid than that of exanthematic typhus. In some cases the spots remain discrete, brownish or purplish, giving a speckled appearance. Slight icteric tinging of the skin and scleræ is frequently observed. In some cases gangrenous patches of skin occur on the elbows, toes and lobes of the ears. During the third week desquamation sets in the eruption gradually fades. (Fig. 44.)

Constipation is the rule. The liver is usually enlarged; the spleen enlarged, firm and tender. Albuminuria is due to kidney involvement, and the highly-coloured, concentrated urine usually contains casts. Severe cases are characterized by œdema of the face and limbs. Nausea and vomiting set in about the beginning of the second week and in fatal cases may persist throughout. Respiration is rapid, owing to respiratory catarrh. The pulse loses in volume as it increases in frequency. The erythrocyte count is little affected; the hæmoglobin content is slightly reduced and there is a mild leucocytosis of 12,000 to 18,000 per c.mm. There is a reduction in the blood-platelet count. Complications, such as gangrene of the tonsils, scrotum and prepuce, are common in the milder form. A high degree of immunity is produced and no instance is known of a second attack.

It is now recognized that there is little evidence for the view that eastern and western types can be distinguished. On the whole, however, in the west the rash tends to be more intense and widely distributed; the febrile period is longer, headache, muscular pains and arthritis symptoms more severe, and the tendency to retinal hæmorrhages more pronounced. The percentage of children attacked is higher in the east than in the west.

Diagnosis.—The sudden onset, the intense muscular and joint pains, together with a negative Widal reaction, help to differentiate it from typhoid. The geographical distribution remains a most important factor in its separation from exanthematic typhus. The serological reactions belong to the indeterminate group. A feeble agglutination with *Proteus OX*19 occurs and also with OX_2 and *OXK*. Guinea-pigs are easily infected and develop the Neill-Mooser reaction, with swelling of the testes and scrotum.

A differential table is given by Cumming and Millam between Rocky Mountain fever and Brill's disease:

Rocky Mountain Fever.	*Endemic Typhus*
Rural.	Urban.
History of tick bite.	Premises infested with rats.
Children.	Adults and middle-aged.
Several cases in the same family.	Sporadic.
Fever up to 107° F., lasts for weeks and ends by lysis.	Fever lower, ends by crisis in second week.
Rash on wrists, then general, including palms of hands and soles of feet.	Rash first on trunk, flexor surface of limbs, rarely on face, palms or soles.
Mortality 25 per cent. or over.	Mortality under 5 per cent.

Mortality varies considerably. In Montana it has been as high as 75–90 per cent. The percentage given by Topping (1941) was 19·4 for the western and 18·1 for the eastern form.

Treatment.—As in exanthematic typhus, treatment, in the absence of any specific remedy, must be on general lines.

Prophylaxis.—Attempts at prophylaxis are being carried out on the basis of the known methods of transmission. War is being waged on ground squirrels and woodchucks, the natural hosts of *D. andersoni*. Domestic stock, especially sheep and goats, are being systemically dipped with arsenicals, to prevent the spread of the tick. It must be borne in mind that *D. andersoni* does not infest human dwellings.

On the whole, the sheep is an uncongenial host, and badly infected districts should be converted into sheep-runs. Workers in endemic areas should be clad in a one-piece costume, the trousers should be tucked inside woollen socks and the sleeves secured with a strap at the wrists. Tick bites should be immediately cauterized or, if possible, excised. *D. variabilis* is frequently brought into houses by house dogs, which may be freed from infection by the application of powdered derris root. (The introduction and acclimatization to U.S.A. of the hymenopterous insect *Ixodophagus*, which preys on these ticks, as advocated by Brumpt, has proved unsatisfactory.)

Tick paralysis.—Hadwen first described the tick—*Dermacentor andersoni*—in the dry districts of British Columbia as giving rise to a pecular paralysis which may prove fatal, and in these same districts it may affect man and other animals. Todd at a later date found that similar symptoms were produced by the bite of *Hæmaphysalis cinnabarina* and apparently in South Africa by *Ixodes pilosus*, and in Queensland by *I. ricinus* and *I. holocyclus*.

Hadwen's observations were subsequently confirmed by Nuttall in Cambridge. In experimental cats and dogs epileptiform convulsions may be produced. This form of disease is manifestly different from Rocky Mountain fever and actual causation of the paralysis is not clear. It may be some form of toxin. The wounds made by these ticks are particularly painful.

VI. BULLIS FEVER (Lone Star Fever[1])

A new form of rickettsiasis appeared in Texas in the spring and summer of 1942 in soldiers engaged in field exercises at Camp Bullis, near Houston, Texas. Henceforward it should be known as "Bullis fever." All patients had multiple tick bites by *Amblyomma americanum* shortly before the onset. The fever lasted from 3 to 13 days in a series of 33 cases. The onset was abrupt, with post-orbital and occipital headache, and the fall of fever was by lysis. General adenopathy was common. In the more severe attacks, a maculo-papular rash appeared on the trunk, in some resembling murine typhus, in others like German measles; it never lasted more than 48 hours. On the second or third day there was pronounced leucopenia, with associated neutropenia (Woodland, McDowell and Richards, 1943). Later, Anigstein and Bader (1943) isolated from a collection of *Amblyomma americanum* an intra-cytoplasmic rickettsia which was established in guinea-pigs. Cross immunity tests indicated that the organism is not identical with *R. rickettsii* or *R. burneti*. This has now been confirmed by Livesay and Pollard (1943).

Anigstein suggested that originally Bullis fever might be mite-borne and the disease related to tsutsugamushi, because the two entities are the only rickettsiases showing generalized lymphadenopathy and leucopenia. The scene of the epidemic described was heavily infested with *Trombidium irritans*, the American chigger, or harvest-bug. This discovery therefore has interesting implications. It may be that it is the same entity as

---

[1] *A. americanum* is popularly known as the "Lone Star tick" from the bright spot on the scutellum

Colorado tick fever, which somewhat resembles dengue (Topping and colleagues, 1940).

VII. TICK TYPHUS (FIÈVRE BOUTONNEUSE) TICK-BITE FEVER

Synonyms. Marseilles fever; eruptive fever; *fièvre exanthematique; escharo nodulaire;* tick-bite fevers—South African, South American and Indian forms.

History.—*Fièvre boutonneuse* was first described by Conor and Bruch in 1910 in Tunis, but is now known to occur throughout the Mediterranean littoral, and also in Marseilles and many other districts in Southern France, as well as in Italy, Portugal, Spain, Greece and Roumania. It has been reported on the Guinea Coast by Blanc, from Senegal by Peltier and Carrière, and from Sierra Leone by Gordon and Davey (1936).

Distinctive features.—The distinctive features of this fever are that the virus is transmitted by the common dog-tick, *Rhipicephalus sanguineus* (Durand, Conseil, Brumpt, 1930) and that the dog constitutes the reservoir of the virus, for these animals have been shown to be susceptible and their blood infective both for man and monkeys (Durand). The tick-transmitted virus (*Rickettsia prowazeki* var. *conori*) passes hereditarily from one generation of tick to another without necessarily passing through a reservoir animal.

Another distinctive feature is the appearance of a primary sore at the site of the infecting tick-bite which, becoming gangrenous, is known as "*tache noire*", and varies in size from a pin's head to a pea, but is not usually painful. Lymphangitis subsequently occurs. These features are comparable with those of tick-bite fever of South Africa (Troup and Pijper, 1931) and of tsutsugamushi.

At first French investigators hesitated to include it in the typhus group on account of discrepancies in the Weil-Felix reaction, but this has been cleared up. The Neill-Mooser reaction in guinea-pigs is positive, especially when an emulsion of infected ticks is injected (Caminopetros, 1932). No cross immunity exists between *fièvre boutonneuse* and endemic (flea-borne) typhus, and the former appears to be definitely a local form of tick-borne typhus. In other respects it resembles Rocky Mountain spotted fever, but the rash (Plate VII, 8) tends to be papular as well as petechial. There are now strong reasons for believing that it is closely related, in mode of transmission and ætiology, with the spotted fever groups of North America (p. 240).

African form.—The tick-bite fever of South Africa, East Africa and South Abyssinia originally described by McNaught in 1911, and again by Pijper and Dau in 1934, resembles *fièvre boutonneuse*, but is conveyed by larval ticks—*Amblyomma hebræum, Rhipicephalus appendiculatus* and *Boophilus decoloratus.* Sporadic cases are reported from Johannesburg, Kenya and Southern Abyssinia. These small ticks climb on to grass, attaching themselves to man and animals and, being veld dwellers, are not found in houses or on domestic animals. The disease in this respect resembles Rocky Mountain fever. In nature, infection is conveyed by tick-bite, and rickettsia can be demonstrated in the Malpighian tubules of the ticks; an emulsion produces the disease in animals and a slight Neill-Mooser reaction in guinea-pigs. The serum reactions in man are not quite clearly cut. In most cases *Proteus OXK* is agglutinated in a higher titre than *OX*19. Pijper and Crocker (1938) have shown that the virus of tick typhus does not immunize against the exanthematic or murine forms.

Two forms of South African "tick-bite fever" are described: mild, or abortive, and fully developed. In the first the only symptom may be the primary sore, accompanied by adenitis and lymphangitis at the site of the bite. In the fully-developed form, in addition to the primary manifestations, the fever lasts ten days, with severe headache, stiffness of neck, conjunctivitis and petechial rash on the fifth day. It is apt to be confused with cerebro-spinal meningitis, measles and typhoid fever.

Gear and Douthwaite regard the dog as the reservoir of infection in South Africa, especially in the Cape Province, where it is suggested that the local dog-tick *Hœmaphysalis leachi* may transmit the infection.

South American form.—South American tick typhus, sometimes known as Tabardillo, or "burning fever," is a form of tick typhus common in Minas Geraes, Brazil (Magalhaes, 1940); it resembles *fièvre boutonneuse* and may be the analogue of Rocky Mountain fever farther north, as Parker, Davis and Dyer have shown that there is cross-immunity; it is possibly the same as the disease which has occurred in Colombia and Texas (*see* p. 241). It is chiefly rural. Montiero succeeded in transmitting the virus through the tick *Amblyomma cajennense*, and produced intraocular lesions in guinea-pigs and monkeys by the injection of infected human blood, and it has been possible to demonstrate rickettsiæ in the endothelial cells of Descemet's membrane.

The mortality is said to be high—about 80 per cent. Ambulatory forms are recognized. There is usually a local lesion and adenitis. The grave forms are associated with sudden onset, severe pains, vomiting and delirium. Magalhæs found a leucocytosis up to 59,800 per c.mm. in 74 per cent. of the cases; leucopenia is exceptional; and in severe attacks the blood urea is as high as 205 mgm. per cent. The urine is scanty, urea content diminished and there is chloride retention in the majority of cases. The Weil-Felix reaction is not clear-cut (Fialho, 1932); agglutination with *OX*19, *OX*$_2$ and *OXK* is found in low dilutions. Dias (1938) stated that the natural reservoirs are the opossum, domestic and wild dog (*Cerdocyon thous*), the wild rabbit (*Sylvilagus brasiliensis*) and the agouti (*Dasyprocta*). The tick vectors are several species of *Amblyomma*:—*A. cajennense*, *A. striatum*, *A. brasiliense*; the former especially, according to Dias, is commonly parasitic on the domestic dogs.

Indian form.—McKechnie (1911) found a mild sporadic form of typhus in the Kumaon Hills on the North-West Frontier districts of India, and Megaw (1916) suffered from such an attack which he attributed to the bite of a tick. Other cases have been reported by Stott (1935) from Lucknow and by Webster (1939) from the Simla hills. The serum agglutination against *OXK* is said to be marked. Other cases giving this reaction have been recorded from Lahore, Meerut, Bengal, Assam and Bombay (Boyd) (*see* p. 287). The tick vector is unknown. On the other hand, this may be a form of mite-borne typhus, *Trombicula deliensis* being suspected.

VIII. "Q FEVER"

History.—A new fever was noted in 1935 in meat-workers in Brisbane, Queensland, by Burnet and Freeman, and since then many cases have been described. By 1939 it had been realized by Dyer and his collaborators that the organism—*Rickettsia burneti*—is the same as that described in America as *R. diaporica*, which is spread by the ticks, — — *andersoni* and *Ornithodorus turicata*, in Wyoming and the Western United States.

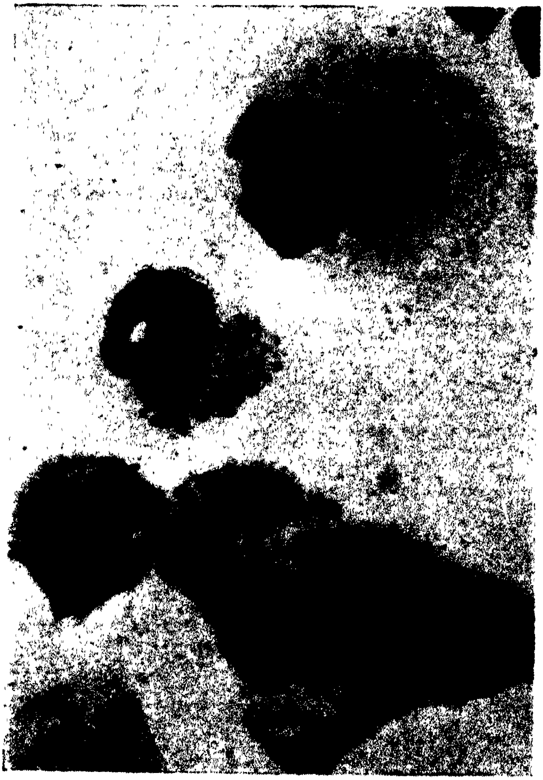


Fig. 45. *Rickettsia burneti (diaporica)*. **American Q Fever.**
(Wyoming, U.S.A.)
prepared from peritoneal scrapings of infected
L. Anigstein, Galveston, Texas.) Giemsa. ×

Geographical distribution and epidemiology.—Q fever occurs in Queensland and is apparently widespread in America. There is no obvious relationship to season. Most cases have been noted in meat-workers or dairy farmers.

Ætiology.—*Rickettsia burneti* is morphologically identical with *R. prowazeki* and produces characteristic pathological effects in monkeys and mice. There is a well-defined febrile reaction, during which time the blood is infective for guinea-pigs. Mice inoculated intraperitoneally show enlargement of liver and spleen with characteristic histological changes. In sections and smears of infected mouse liver and spleen large numbers of rickettsiæ occur in relatively large intracytoplasmic colonies (Fig. 45).

R. burneti can be cultivated on minced chicken embryo and reaches its maximum growth during the second week. When eight or nine-day embryos are inoculated and membranes removed after six days and incubated at 34° C, numerous rickettsiæ are visible. After numerous passages on egg-membrane the American strain showed no reduction in virulence for guinea-pigs. Cox and Bell similarly cultivated the American strain in chicken embryo, in flasks containing yolk sac tissue suspensions and filtered human ascitic fluid, in which it develops more profusely than does the Australian virus.

The natural reservoir in Queensland is the bandicoot (*Isoodon torosus*), which is very susceptible to experimental infection.[1] Smith and Derrick (1940) isolated the rickettsia from a tick, *Hæmaphysalis humerosa*, which is normally an ectoparasite of the bandicoot and opossum. More recently (1942), Derrick and Smith found that cattle may play an important part in transmission, and that human infection may result from direct infection from the body tissues of infected cattle, or further indirect infection from infected cattle by the body tissues of ticks, especially *Boophilus annulatus microphis*.

Since 1938 it has been ascertained by Davis, Cox, Dyer and others that the organism, *R. diaporica*, which was first isolated from the tick, *Ornithodorus turicata*, is identical with *R. burneti* and should be known as *R. burneti* var. *americana*. Davis (1940) showed that it may persist in the tissues of this tick for three years. Since then, outbreaks of Q fever have occurred (Hornibrook and Nelson), and this organism has been recognized in ticks, in Montana, Wyoming, Oregon and California. The principal vector in these districts is *Dermacentor andersoni*. Similarly, Smith and Derrick ascertained that *R. burneti* exists as a natural infection in the tick *Hæmaphysalis humerosa* in Australia. The range of susceptible hosts is the same in both varieties, but the American (Montana) strain appears to be more virulent except for mice. There is some evidence that congenital transmission may take place in the tick.

Burnet and Freeman confirmed the findings of Dyer that the *R. burneti* of Australia and of America are identical. Both Montana and Australian Q strains are agglutinated to the same titre by sera from a number of animals experimentally infected with one or other strain. Sera from man and animals infected with other rickettsial diseases do not agglutinate *R. burneti*. Guinea-pigs protected against Rocky Mountain fever are not immune to Q fever, but protection against Q fever is active against the virus recovered from wood ticks (*D. andersoni*) in Montana, and the serum of patients recovered from Q fever protects against both

---

[1] This animal is a marsupial and is quite distinct from the bandicoot rat (*Nesokia bandicota*).

Australian and American strains. The serum of man or animals infected with *R. burneti* does not agglutinate any strain of *Proteus*. As with other rickettsial infections, mixtures of virus and immune serum in suitable proportions may be injected into animals without febrile response, but in all instances the subsequent complete immunity of the animal indicates that actual infection has indeed taken place.

R. burneti is present in the blood of man during the fever period only, but may be found in the urine during the later stages. Burnet and Freeman demonstrated that the virus is filtrable, though with difficulty, through relatively permeable (0·7 μ) gradocol membranes.

Agglutination reaction of rickettsial suspensions by human monkey and guinea-pig sera occurs and is specific, and agglutinins are present in the serum of man and animals for several months after an attack. There is no cross-immunity between this disease and typhus or Rocky Mountain fever (Pinkerton, 1940). The disease produced in the guinea-pig is mild and mortality is nil, but when the animal is killed the spleen is found enlarged. One attack in the guinea-pig confers immunity and this has proved a method for the diagnosis of Q fever. In America these animals are readily infected by the fæces of the tick, *Ornithodorus turicata*. Rats are mildly susceptible, though the albino variety and rabbits are resistant.

Symptoms.—This fever is known in America as " Nine-mile fever." The onset in man in acute and sudden. The course and duration vary considerably. Sometimes there is a rapid defervescence after six to nine days ; sometimes the course is protracted to the third, or even to the fourth week, and the temperature falls by lysis. There is no rash as in other forms of typhus. The outstanding symptom is headache, which may be extremely severe and persistent, while the pulse-rate is slow. The disease is comparatively mild and there have been no fatalities.

Hornibrook and Nelson reported an outbreak in 15 persons amongst 153 employed in one building in North America. No valid evidence was obtained in this instance that any arthropod was concerned with this outbreak, or in the transmission of the disease. It is very suggestive that central pneumonia, or pneumonitis, has been observed as a complication in a number of cases in America. It is assumed that this illness may not be uncommon and may have a wider distribution than hitherto supposed.

Findlay found that intranasal instillation of *R. burneti* (American and Australian strains) in mice causes interstitial pneumonia. These lesions are similar in character to those produced by similar applications of the rickettsiæ of exanthematic and murine typhus.

Diagnosis.—An agglutination test with suspensions of Rickettsiæ grown on egg-sac is now employed and is highly specific. Agglutinins are present in the serum for several months after an attack. A complement fixation test was employed by Bengtson. The serum of patients, as well as that of infected monkeys and rabbits, does not agglutinate *Proteus* *OX*19, *OX*$_2$, or *OXK*.

Treatment.—In the present state of knowledge this is symptomatic.

Prophylaxis.—Burnet and Freeman found that the virus, when mixed with immune serum or treated with lauryl sulphate, confers immunity after inoculation, and so also do suspensions of rickettsiæ killed by heat or treated with formalin. The appearance of fever in abattoir workers has now been explained as due to handling meat of infected cattle. It is therefore obviously important that all meat workers should be protected by prophylactic inoculation.

PROPHYLACTIC INOCULATION OF THE TYPHUS GROUP OF FEVERS

A vaccine, to be of real value in the control of rickettsial infection, must produce a high degree of immunity which lasts for a considerable time ; must not evoke dangerous reactions ; and must be easily produced and easily administered.

Killed exanthematic typhus vaccine.—The earliest and most widely used method is that of Weigl. This vaccine is prepared from the intestinal contents of lice injected *per rectum* with suspensions of living *Rickettsia prowazeki*. After an interval the lice are killed and the intestines removed and ground up with dilute formol-saline. This method has been employed in Poland and in Germany. A very considerable number of lice—between 200 and 300—is required to immunize a single individual, and the cost is great. Recent reports from Germany emphasize the fact that a death from louse-borne typhus has not yet been recorded in a patient fully immunized with Weigl's vaccine. The difficulty of rearing large numbers of lice renders the use of the Weigl vaccine on a wide scale impracticable.

Killed tick-typhus vaccine.—A method in which the tissues of infected *Dermacentor andersoni* are used has been employed by Spencer and Parker since 1925 in vaccination against Rocky Mountain spotted fever ; 150,000 people had been inoculated by 1935, and Parker (1941) stated that amongst persons infected within one year the mortality was only 8·11 per cent. as compared with 82·35 per cent. amongst unvaccinated controls. Similarly, Monteiro (1933) used the tissues of infected *Amblyomma cajennense* as a vaccine against São Paulo typhus.

The chief difficulty lies in obtaining rickettsiæ in large enough numbers. Numerous methods have been used : e.g., rickettsiæ have been grown in serum with Tyrode's fluid containing chick embryo tissues, but the growth, which is at first luxuriant, cannot be maintained. Cox utilized a method of injecting rickettsia (from typhus, Rocky Mountain spotted fever, *fièvre boutonneuse* and Q fever) into the yolk sac of the developing chick embryo, which yields a rich growth. Formalized or carbolized suspensions obtained by this method have been used recently in Spain. By this method one dozen eggs yield 100 c.c. of vaccine, enough for about thirty people. The ultimate results of this method are still under trial. This vaccine is very widely used in N. Africa in the present war.

Cox's vaccine can be produced in large quantities. The virus is grown in developing fowl embryo and is transferred to other fertile eggs by 0·5 c.c. of 5–10 per cent. suspensions of yolk sac in 50-50 mixture of sterile beef infusion broth, or by using an equal quantity of undiluted yolk fluid. The latter method is preferred for the preparation of vaccines. The maximum multiplication is not usually obtained before 4–6 passages.

Formalized suspensions of the rickettsiæ are then prepared, and have been found to be stable on storage. This method is at present under trial. The vaccine is injected three times (0·5 c.c. once and 1 c.c. twice) at five-day intervals.

The customary methods so far employed as a means of testing the efficacy of typhus vaccines are active immunization of guinea-pigs, agglutination tests for *Proteus OX*19, and neutralization of antibodies in the serum of inoculated subjects.

The protection afforded seems to be only partial. Recently (1943) Van den Ende and others published a report of an outbreak of murine typhus in twelve laboratory workers who had been immunized previously with Cox's vaccine. The infection was contracted by the respiratory route. The disease was moderately severe in three cases; mild in others.

Suspensions of rickettsiæ from tissues.—A different method consists of obtaining a rich suspension of rickettsiæ from the lungs of animals infected by the intranasal technique. This consists of setting up a rickettsial pneumonia in mice, in rabbits or, recently in South Africa, in gerbilles, removing the lungs and obtaining by centrifugalization a rich emulsion which is then treated with formalin or phenol. No reactions are caused by the injections, of which it is necessary to administer four or five at intervals of five days. A good immunity is said to be produced against exanthematic typhus, but only partial against the murine form. Castañeda (1941) proposed to use a lung vaccine prepared from rats in a similar manner, and to employ both types of rickettsia in the vaccine.

Living typhus vaccines.—Specially rich emulsions are obtained from the peritoneal fluid of animals irradiated by X-rays and injected intraperitoneally (Zinsser). Laigret in Tunis and his colleagues employed strains of murine typhus passaged in the brains of mice. They are then ground up and dried in egg yolk and sodium phosphate.

Blanc and Baltazard (1940) in Morocco used two distinct methods. In the first the tissues of infected guinea-pigs are ground up in physiological saline, and the emulsion is treated with bile immediately before injection. In the second method the dried fæces of rat fleas (*Xenopsylla cheopis*) are treated in similar manner. It is claimed that in Tunis one-tenth of the indigenous population has been inoculated with the mouse-brain egg-yolk vaccine. This method has been subjected to grave criticism on the grounds that the reactions produced are very severe and that in some cases the clinical picture of murine typhus has been reproduced. The same objections have been raised in Spain to the employment of the Laigret vaccine, and the results have so far been unsatisfactory.

General considerations.—Felix emphasized that, at present, immunization against the typhus group is still in the experimental stage; one of the chief difficulties is to maintain the labile rickettsial antigen in cultures. The best method of killing and preserving the vaccines has yet to be found. At present phenol and formalin are employed, and it is probable that they destroy the labile rickettsial antigen.

Recent reports confirm the impression that egg-yolk and animal-lung vaccines are likely to give some degree of protection to man.

Subsection D.—FEVERS CAUSED BY BACTERIA

CHAPTER XI

PLAGUE

Definition.—Plague is a specific, inoculable and otherwise communicable epidemic disease common to man and many of the lower animals. It is characterized by fever, adenitis, a rapid course, a very high mortality, and the presence of a specific bacterium, *Pasteurella pestis* (*Bacillus pestis*), in the lymphatic glands, viscera, and blood. In a large proportion of cases buboes form in the groins, armpits, or neck.

History.—The first authentic account of plague in Europe describes an outbreak in A.D. 542, which, starting from Egypt, spread over the Roman Empire. The disease visited England as a widespread epidemic for the last time in 1664–79, and in 1664–5 upwards of 70,000 out of the 460,000 inhabitants of the London of that day perished. In the 14th century it was known as the " Black Death " not, as popularly supposed, on account of the petechial nature of the disease, but on account of the " terrible death " it occasioned. From time to time, cases of plague have occurred in the Port of London in seamen from Eastern countries, and plague-infected rats are by no means uncommon in the docks of the metropolis ; but, with the exception of a limited epizootic in rats and rabbits, and several fatal cases in man in 1910 in Suffolk, there is no record of plague in Britain, apart from the cases occasionally seen in the seaports, since the seventeenth century. Plague reappeared in Paris in 1920 after an absence of three centuries.

Geographical distribution.—Probably plague is always present in some part of India and in Uganda, especially among the rude hill-people. It is known to have been endemic in the south-west of China, in the province of Yunnan, for many years. The present extension of plague probably had its origin in that part of China, and it is safe to prophesy that it will continue epidemic in that country for many years to come. Japan and the Philippines were both infected from China.

Imported from Hong Kong, the disease appeared in 1896 in Bombay, and subsequently, as a great epidemic, spread to Calcutta and to many other parts of India, where it still prevails. In 1913 plague spread from Negapatam to Ceylon, and in 1914 broke out in epidemic form for the first time in Colombo, where it remained confined to one portion of the city. India has suffered more than any other country ; there have been years when the plague deaths exceeded a million, and they were considerably above that figure in 1907. It has been estimated that from the time of its introduction into India until that date there was a total of nearly ten million deaths.

Soon after its appearance in India, plague became extensively epidemic in Mauritius, and it still prevails there at certain seasons. Mombasa and British East Africa (including Nairobi), the West African colonies, Madagascar, Delagoa Bay, Cape Town, Port Elizabeth, and Durban, also Sydney and Brisbane in Australia, and Alexandria in Egypt have all been invaded. Plague was introduced into Java in 1910, and has existed ever since in one of the most densely populated areas in the world. There has been an average of 3,000 to 6,000 cases *per annum*.

Until its appearance in Brazil, Argentina, and other South American countries, and in San Francisco and Mexico, plague had never invaded the Western hemisphere ; now it is of considerable importance in California. Peru, into which the disease was introduced from India in 1903, was the first country on the West Coast of South America to be invaded. The infection reached Ecuador through Guayaquil and raged at an altitude of 10,000 feet.

Epidemiology and endemiology.—*Age, sex* and *occupation* have very little influence in plague. The youngest children are susceptible.

Atmospheric temperatures, if very high or very low, seem to have a repressing effect. On the other hand, plague on more than one occasion has flourished during a Russian winter. On the whole, the evidence points to moderate temperature—50° to 80° F.—combined with a certain degree of dampness, as being the principal atmospheric condition favouring epidemic outbreaks and recurrences. In Hong Kong, for instance, it was found by Uttley that a mean temperature of 63° F. with a relative humidity of 83° and aqueous vapour tension of 0·500 favours the spread of plague, but when the temperature reaches 82–83° F. or more, for three to four months, with a vapour tension of 0·900, this disease tends to die out.

In large towns and in some districts in which plague recurs for several years in succession there is a seasonal periodicity (which may not be the same in all places) of maximum and minimum prevalence.

The *duration of epidemics of plague* is very variable. In large cities—Bombay, Hong Kong, Canton, for example—the disease, when fairly established, may not relax its grip for ten or more years. In smaller towns it may disappear in a few months.

The *extension of plague epidemics* is peculiar : the disease follows trade routes, and especially the grain trade. Sometimes it may spread rapidly from point to point ; more generally it creeps slowly from one village to another, from one street or one house to another. Sometimes it skips a house, a village, or a district.

These and many other facts in the epidemiology of plague are to be explained by the connection of the disease with the rat and its fleas, and depend in the main upon the migrations of the former and the breeding seasons of the latter.

ÆTIOLOGY

The micro-organism.—The specific cause of plague is the bacillus which was discovered by Yersin and Kitasato in 1894. It occurs in great profusion in the characteristic buboes, generally in pure culture, although towards the later stages it is often associated with the streptococci and staphylococci of suppuration. It is present, also, in great abundance in the spleen, intestines, lungs, kidneys, liver and other viscera, and, though in smaller numbers, in the blood, while in the pneumonic type it is found in the sputum in profusion. It may be found also in the urine and fæces. Towards the termination of rapidly fatal cases it occurs in great numbers in the blood.

Pasteurella pestis (Fig. 46), as seen in a blood-film, or in preparations from any of the other tissues, is a short, thick cocco-bacillus (1·5 to 2 by 0·5 to 0·7 μ) with rounded ends, very like the bacillus of chicken cholera. A capsule, or the appearance of one, can generally be made out, especially in bacilli in the blood. The organism is readily stained by aniline dyes, especially by Romanowsky stains, the extremities taking on a deeper colour than the interpolar part, giving a bipolar appearance. Epstein regards bipolarity as a phenomenon not specially confined to *P. pestis*; the fixing and staining of the specimen naturally influence the result.

Bhatnagar states that virulent stains of *P. pestis* can be recognized by the abundance of the envelope substance.

It is non-motile, Gram-negative, indol-positive, and gives nitrite reaction with sulphanilic acid and X naphthylamine.

Cultural characters.—When sown on blood-serum and kept at body-temperature, in from twenty-four to forty-eight hours an abundant moist, yellowish-grey growth is formed without liquefaction of the culture medium. On agar, but better on glycerin-agar, the growths have a greyish-white appearance. In agar plate cultures they show a bluish translucence, the individual colonies being circular, with slightly irregular contours and a moist surface; on mannite-neutral-red-bile-salt agar the colonies are bright red, but are colourless on a similar medium in which lactose is substituted for mannite. Litmus-milk and glucose-broth are rendered slightly acid; lactose-broth is unchanged. Young colonies are glass-like, but older ones are thick at the centre and more opaque; they are singularly coherent and may be removed *en bloc* with a platinum needle. Stab-cultures show after one or two days a fine dust-like line of growth. According to Yersin, when sown on gelatin, the bacillus gives rise to white transparent colonies which, when examined in reflected light, present irridescent borders. In bouillon the cultures present a characteristic appearance: the liquid remains clear, whilst a granular deposit takes place on the sides and bottom of the tube. Cultivated on broth in which clarified butter or coco-nut oil is floated, *P. pestis* presents characteristic stalactite growths which gradually fall off, forming a granular deposit. Examined with the microscope, these various cultures show chains of a short bacillus, presenting here and there large bulbous swellings. In gelatin the bacilli sometimes form fine threads, sometimes thick bundles made up of many laterally-agglomerated bacteria, and involution forms are common. The bacillus does not produce spores.

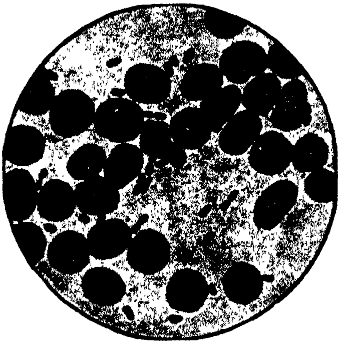


Fig. 46.—*P. pestis* **in peripheral blood in septicæmic plague. 500.** (*Microphotograph: Dr. J. Bell.*)

The most favourable temperature for culture is from 36° to 39° C.

The virus of plague can be modified by artificial methods; it is well known that some process of this kind takes place in nature, for as a plague epidemic decreases, so the case-mortality falls.

Experimental plague.—In the guinea-pig, within a few hours of the introduction of the virus, a considerable amount of œdema appears around the puncture, and the adjacent gland is perceptibly swollen. At the end of twenty-four hours the animal is very ill; its coat is rough and staring; it refuses food, and becomes convulsed and usually dies on the third or fourth day.

If the body is opened immediately after death, a sanguineous œdema is found at the point of inoculation, with hæmorrhagic inflammatory effusions around the nearest lymphatic gland, which is much swollen and full of bacilli. The intestines are hyperæmic; the adrenals, kidneys, and liver are red and swollen. The much-enlarged spleen frequently presents an eruption of small whitish granulations resembling miliary tubercles. All the organs, and even any serous fluid that may be present in peritoneum or pleura, contain plague bacilli. In the blood, besides those free in the liquor sanguinis, bacilli are found in the mononuclear, though not, it is said, in the polymorphonuclear leucocytes.

Rôle of the rat in plague.—Although small and circumscribed epidemics of plague may occur without the intervention of the rat, as when it first appeared in Colombo, there can be no doubt that in most

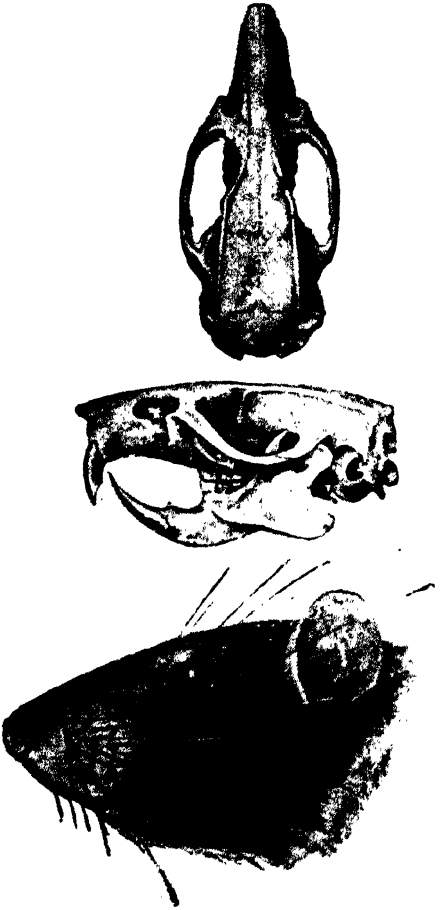


Fig. 47. ***Rattus norvegicus.***

Configuration and anatomical characters of head and skull (nat. size).

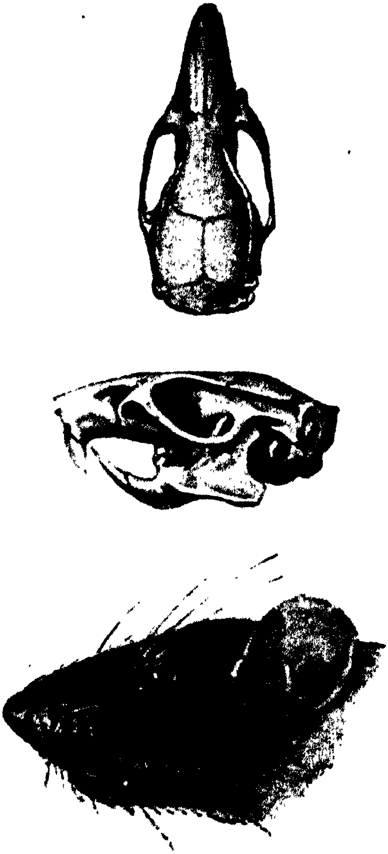


Fig. 48.—***Rattus rattus.***

Configuration and anatomical characters of head and skull (nat. size).

epidemics of the bubonic form this rodent plays an important part, both in the introduction and in the spread of infection. The species principally concerned are *Rattus norvegicus* (or *decumanus*), the grey rat, and *Rattus rattus*, the black rat (Figs. 47 and 48). The mouse, *Mus musculus*, is also susceptible. The bandicoot and musk rat are of little importance in these respects, although susceptible to laboratory infection. In Bombay the epizoötic appears first in the *Rattus norvegicus* community, *Rattus rattus*—the more domestic species—being subsequently attacked. Later the disease appears in epidemic form in man (Chart 13).

The seasonal prevalence of bubonic plague in rats is marked, and is not due to a periodicity in their reproduction, but is connected with periods in which fleas are most numerous.

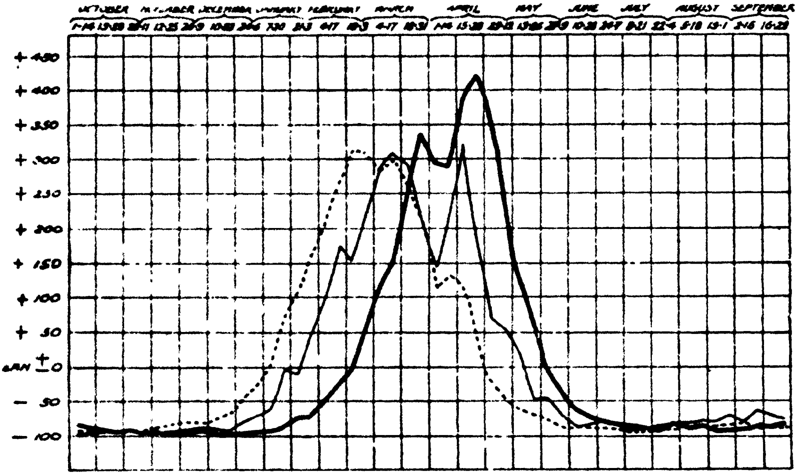


Chart 13. Showing progress of plague in rats and man.
("*Report of Indian Plague Commission.*")

············ Infected *R norvegicus*.
———— Infected *R. rattus*.
▬▬▬▬ Human deaths from plague.

In places in which plague epidemics keep recurring year after year the local rats acquire a considerable degree of immunity; moreover, this is transmitted hereditarily. Thus, in plague-free towns in India—e.g. Madras and Dacca—the mortality among the local black rats experimentally infected was 100 per cent., while in plague-stricken towns, such as Cawnpore and Poona, it was much less.

Another observation which may have important bearings on the spread of plague, and the yearly recurrence of epidemics in the same place, is that in certain rats the disease may assume a chronic form.

Other animals may die of plague during an epidemic; dogs are said to be immune.

Selvatic or wild rodent plague.—Formerly, epidemiologists concerned themselves mainly with rat epizoötics, but recently, increasing attention is being paid to plague of wild rodents of the fields and woods—

field-rodent, or selvatic, plague. It is now realized that plague exists in a smouldering state over vast tracts of territory among the Asiatic marmots; among the "susliks," mice and jerboas of the desert region of south-eastern Russia; among the gerbilles and *muridæ* of the African high veld and coastal region; among the chipmunks and ground-squirrels of California; and in South America among the cavies ("cuis," wild guinea-pigs), and other peculiar rodents of the Pampas. In Chile, on the other hand, plague is restricted almost entirely to rats in the seaports. Desert country is unfavourable to the rat flea, *Xenopsylla cheopis*. Although field-rodent plague has given rise so far to comparatively little human mortality in most countries, in North Manchuria, where the disease is endemic in the marmot or "tarabagan," virulent epidemics of *pneumonic plague* have occurred.

Rôle of the marmot and other rodents.—Mongolian and Siberian pneumonic plague epidemics are associated with the occurrence of the disease in species of marmot known as "tarabagan" (*Arctomys bobac*, Fig. 49),[1] and several smaller species (*Citellus citellus* and *C. mugozaricus*), locally known as "susliks," which can harbour the plague bacillus in their bodies without apparently suffering any ill effects during hibernation, thus constituting a more or less permanent reservoir of the plague virus. Possibly plague infection is transmitted to man by the fleas which infest these animals, but it is more generally considered that the rodent fleas play a minor part and that the infection is transmissible *via* the alimentary tract. It has been shown that in hibernating spermophiles *P. pestis* loses its virulence and is less easily cultivated. Epizoötics of plague in these regions generally begin after hibernation.

The pouched marmot of the Caucasus (*Spermophilus guttatus*) is extremely susceptible to plague infection, and is probably concerned in the spread of the disease in that region. In Transbaikalia plague occurs in *Spermophilus eversmani* and in *S. dauricus*, which are 22 cm. long and rather resemble the tarabagan. The presence of spermophiles, which are related to marmots and ground squirrels, can be determined by the characteristic excrement at the mouth of their burrows.

As an indication of the important part that many animals play in the spread of human plague, extracts from the report of the first Plague Congress of Soviet Russia, 1927, may be taken as an example. In South-East Russia, from October, 1925, to May, 1927, there were 42 plague epidemics with 310 cases. The infection of 11 of these originated from domestic and field mice, four from spermophiles, three from jerboas (*Dipodipus sagita*), and four from gerbilles (*Rhombomys opimus*), while seven outbreaks were traced to infection at slaughter of plague-infected camels. Fleas capable of biting man were found on nearly every rodent, and play an active part in the spread of plague in Russia. Proventricular blocking (*see* p. 262) with the plague bacillus occurs in the gerbille fleas (*Ceratophyllus tesquorum* and *C. lævіceps*).

Plague is known to exist in the seven western states of America, but it has not so far been noted east of Wyoming nor south of Utah, save in

---

[1] A subspecies of *A. bobac*, *Arctomys centralis*, was found infected in the Narinsk epidemic of 1929–30.

California; the most northerly point is some 150 miles north of the Californian border. In California the ground-squirrel (*Citellus beecheyi*, Fig. 50), although it does not live near human habitations, infects rats that do, and thereby acts as an important reservoir of *P. pestis*.

Seven species of ground-squirrel are now known to harbour plague, including *Citellus beecheyi*, *C. fisheri*, *C. grammurus*, and *C. townsendi*. Other wild rodents from which plague-infected fleas have been collected include a tree-squirrel (*Sciurus douglasii*), chipmunks (*Tamias sp.*), marmots (*Marmota flaviventer nosophora* and *M. fl. engelhardti*), and also prairie dogs (*Cynomys parvidens*). Eskey and Haas have pointed out that wild rodent plague in the Western United States is not always accompanied by infection of domestic rats.

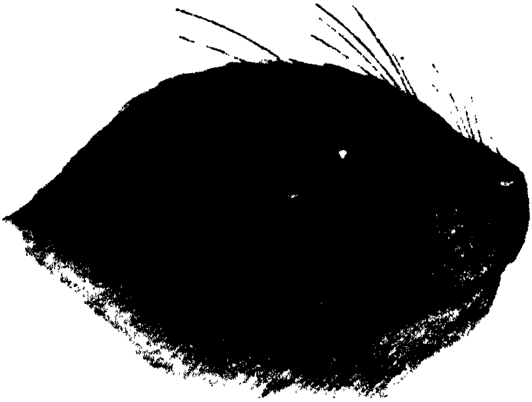


Fig. 49.—*Arctomys bobac*, Siberian marmot

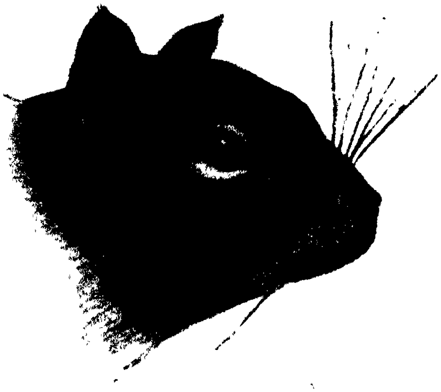


Fig. 50.—*Citellus beecheyi*, ground-squirrel of California (nat. size).

In South Africa, especially in the Cape Province, the rodents of the inland veld have become infected with plague, and by continuously passing the disease from one to another constitute a persistent and dangerous source of human infection. On the high veld the gerbilles (*Taterona lobengulæ* and *Desmodillus auricularis*), the ground-squirrel (*Geosciurus capensis*), and the multimammate mouse (*Mastomys coucha*) are the most important—the latter forming a link by conveying infected fleas from gerbille burrows into human habitations. In the lower bush country the striped mouse (*Rhabdomys pumilio*) plays the chief rôle, while the springhaas (*Pedetes caffer*), a giant jerboa, on account of its extreme mobility, is capable of widely disseminating plague. Two carnivores, the suricate and the yellow mongoose, are susceptible to plague by feeding on dead and dying rodents, and it has been pointed out by Mitchell that the discovery of gerbille remains in the fæces of these animals is a valuable indication of the existence of a rodent epizoötic in the veld districts, as these animals do not normally eat gerbilles unless they are sick.

South African rodents harbour a large number of species of flea. Of these, three, *Dinopsyllus lypusus*, *Chiatopsylla rossi* and *Xenopsylla eridos* have been found, under experimental conditions, capable of conveying plague infection.

To be effective, the prophylaxis of plague in the wilder regions of the world necessarily entails a knowledge of the habits of these rodents. The ground-squirrels are really spermophiles which constitute a connecting link between the true squirrels and the marmots. Ground-squirrels are generally found in prairie-like regions, where they construct an intricate system of burrows, at the main entrance of which they may be commonly seen standing on guard upright and motionless.

The true marmots, such as the "tarabagan," are characterized by the rudimentary thumb, small eyes and ears; the tail is bushy and comparatively short. The burrows which they excavate are very deep and are crowned by mounds of earth thrown up by successive generations of marmots and are known as "bootans" in Mongolia. The gerbilles are small jerboas; they are rather smaller than the domestic black rat; the hind legs are long, the front very short. They are pale fawn with white bellies. Their habitat is sandy country where they live in families. Their warrens extend over an area of 30 square yards and to a depth of 3–4 feet. Gerbilles may commonly be seen sitting warily in an upright position at the mouth of their burrows with front paws extended horizontally. The warrens often harbour ground-squirrels, suricates and mongooses, all four species, apparently, living on friendly terms. Plague is spread among gerbilles (*Taterona lobengulæ*) through the intestinal tract by the cannibalistic habits which these creatures develop when sick.

The multimammate mouse is the wild mouse of the veld and has much the same habits; in country districts it invades human habitations. The striped mouse is diurnal and is more numerous in bushy country, where it usually builds big nests of sticks on the surface of the ground and lives in large families.

In Dakar (Senegal) a shrew (*Crocidura stampflii*), on the Gold Coast, the giant rat (*Cricetotomys gambianus*), and in Kenya the field rat (*Arvicanthus abyssinicus*) play a part in the dissemination of plague.

In South America, in the Argentine pampas, Uriarte and Villazon have shown on several occasions that rodents of the cavy type suffer in plague epizoötics. The species specially concerned are *Microcavia australis* and *M. galea*; a cricelid also, *Graomys griseoflavus*, has been shown to be experimentally very susceptible. It is arboreal, and recently de la Barrera found a small outbreak of human plague which was traced to this animal.

On observations such as these the modern quarantine against plague has been framed.

Rôle of the flea in plague.—It is now known that plague is not communicable from animal to animal by simple contact, but is readily communicated by fleas, and principally by *Xenopsylla cheopis* (Fig. 896, p. 995), the rat-flea of the tropics, *Ceratophyllus fasciatus*, the rat-flea of temperate climates, and *Ctenocephalus canis* and *C. felis*, which bite men, dogs and rats indifferently. These act as passive intermediaries and carriers of the bacillus. *P. pestis* multiplies in the stomach of the flea, retaining its virulence for over twenty days, and is then passed out in the fæces, so that the flea serves not only as a carrier, but also as a multiplier of the germs. Wu Lien Teh has shown that in outbreaks of plague in Manchuria the human flea (*Pulex irritans*) may convey the bacillus direct from patient to patient without the intervention of the rat.

Especially convincing are the experiments of the Indian Plague Commission, which clearly showed that, if fleas are excluded, healthy rats will not contract the disease, even if kept in intimate association with plague-infected rats. Young rats may even be suckled by their plague-stricken mothers and remain healthy. It suffices to transfer fleas from a plague-infected to a healthy animal, or to place the latter in a room in which plague rats have died recently and been subsequently removed. The fleas that have left the body of the dead rats, remaining in the room, convey the bacillus. An animal placed on the floor cannot be infected if the precaution is taken to surround the cage with "tangle foot," so as to keep off the fleas; but if it be placed on the unguarded floor, either in its cage or allowed to run about, or even if suspended 2 in. above the floor--a distance not beyond the saltatory powers of the flea—it will become infected.

Martin and Bacot found that a proportion of the fleas fed on plague-infected rats develop a peculiar condition of stomach and œsophagus, which become blocked with blood-clot containing a pure culture of *P. pestis*. When such a flea feeds on a normal rat, part of the culture regurgitates and communicates infection; at the same time bacilli are passed in the fæces and may infect through any existing abrasion. They further observed that the "blocked" fleas died very rapidly, apparently of thirst, if placed in a warm, dry atmosphere (Fig. 51). There is apparently little difference between wild rodent and domestic rat fleas in the readiness of infection. The life-span of the infected flea is comparatively short: according to Eskey and Haas the average survival is only about 3·2 days. Under experimental conditions some of the squirrel fleas become blocked as readily as *X. cheopis*.

In temperate climates fleas are most numerous during the warmer weather; hence, summer and autumn are the bubonic plague seasons. In warm climates bubonic plague is most likely to become epidemic when temperature ranges between 10° and 30° C.—temperatures favourable to the multiplication and activity of the flea. Temperatures over 30° C. are unfavourable, especially if the atmosphere is dry. Pneumonic plague, not being spread by this insect, is not influenced by temperature in this way.

The flea, then, communicates plague either by its fouled mandibles, by regurgitation, in the act of sucking, or by provoking scratching and consequent inoculation of the bacilli deposited in its fæces.

The capacity of a flea's stomach is about ½ c.mm., and in most cases of human bubonic plague there are not sufficient plague bacilli in the peripheral blood-stream to infect it with any regularity, except in the terminal stages of fatal cases. The "cheopis index" is regarded as important by sanitarians, *i.e.*, the number of fleas per rat. An index of over 5 is likely to produce an outbreak of bubonic plague. The human flea, *Pulex irritans*, which occurs in enormous numbers, especially in Morocco, may become infected; but there is no convincing evidence to show that it ever plays a dominant part in the spread of plague.

It has long been known that large tracts of country and important cities in India, such as Madras, have remained immune from plague, though in constant communication with plague-infected centres. In 1914 Rothschild and Jordan pointed out that the rat-fleas of Indian cities belonged to three closely allied species—*X. cheopis*, *brasiliensis*, and *astia*—and soon afterwards Hirst and Cragg pointed out that in those districts in which plague was uncommon *X. astia* replaced *X. cheopis* as the common ectoparasite of the rat. From this and other experimental evidence it is now assumed that this species is unable to convey the plague infection in the same manner as *X. cheopis* (*see* p. 997).

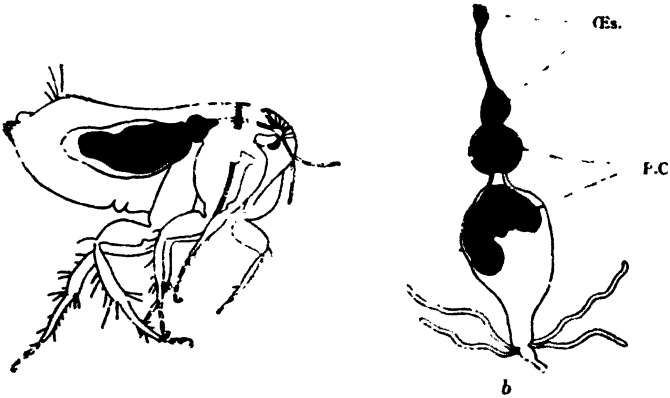


Fig. 51.—*a*, **Flea viewed as a transparent object; the proventriculus and stomach contain a mass of plague-culture.** *b*, **Flea's stomach, obstructed by growth of plague-culture.**

Œs., Distended œsophagus containing fresh blood; P.C. obstructing mass of plague-culture. This figure illustrates the method of transmission of *P. pestis* by *Ceratophyllus fasciatus*. (*By permission of Sir C. J. Martin, "Journ. of Hyg.," 3rd Plague Suppl., Jan.*, 1914.)

Bionomics of the rat-flea.—In ordinary circumstances the rat-flea completes its developmental cycle in from fourteen days to three weeks, but in warm damp weather this may be shortened to ten days. It requires ideal tropical conditions for propagation.[1] The average life of a flea, separated from its host, is about ten days, but it is capable of remaining alive without food for two months should the temperature of the air be low. In tropical temperatures the insect can harbour the plague bacillus without feeding on blood for forty-five days. In Madagascar it has been shown that rat-fleas (*X. cheopis*) may survive in dust, and spread infection long after the bodies of the defunct rats have disappeared.

Apart from the very serious danger arising from vermin infected with chronic plague, which may hang about a house, the house itself does not retain the infection for any length of time. The Plague Commission has shown that floors of cow-dung contaminated with *P. pestis* do not remain infective for more than forty-eight hours, and that floors of "chunam" cease to be so in twenty-four hours.

---

[1] *X. cheopis* can flourish in northern countries in superheated houses and factories, as in U.S.A. and even during the winter months.

Evidence of rat-mortality is not always conspicuous, even when the epizoötic is severe. Dead rats may not be found in the open, but many may be discovered if search is made in the right places. Black rats which live in the roofs of native houses usually fall down on to the floor when stricken with plague.

Pathology.—After death from plague the surface of the body very frequently presents numerous ecchymotic spots or patches. The number and extent of these vary, apparently, in different epidemics. In some epidemics the cutaneous hæmorrhages have been both extensive and numerous. The characteristic buboes are generally apparent; occasionally there are also furuncles, pustules, and abscesses. Rigor mortis is usually moderate; sometimes post-mortem muscular contractions, like those in cholera, take place. Post-mortem rise of temperature is often observed. Decomposition is said to set in early.

The characteristic appearance of plague in a necropsy is that of engorgement and hæmorrhage, nearly every organ of the body participating more or less. There is also parenchymatous degeneration in most of the organs. The brain, spinal cord, and their meninges are markedly congested, and there may be an increase of subarachnoid and ventricular fluid. There are numerous and pronounced puncta cruenta on the brain sections; occasionally there may be considerable extravasations of blood into the substance of the brain (mesencephalon and medulla oblongata).

Ecchymoses are common in all serous surfaces; the contents of the different serous cavities may be sanguineous. Extensive hæmorrhages are occasionally found in the peritoneum, mediastinum, trachea, bowel, stomach, pelvis of kidney, ureter, bladder, or in the pleural cavities. The lung frequently shows evidences of bronchitis and hypostatic pneumonia; sometimes hæmorrhagic infarcts and abscesses are found. The right side of the heart and the great veins are usually distended with feebly coagulated or fluid blood. In pneumonic plague the superficial lymphatic glands are not enlarged; the pleural cavities contain blood-stained serum; the infected lungs are deeply congested and œdematous, and at a later stage pneumonic consolidation is found. The bronchi contain blood-stained serum, and the bronchial glands are swollen and hæmorrhagic.

The liver is congested and swollen and its cells are degenerated and may be the seat of miliary plague abscesses. The spleen is enlarged to two or three times its normal size. The kidneys are in a similar condition. The mucosa of the alimentary canal as a whole is congested, showing here and there punctate ecchymotic effusions and, occasionally, hæmorrhagic erosions, and even–especially about the ileo-cæcal valve—ulcerations.

The lymphatic system is always involved; around the glands there is much exudation and hæmorrhagic effusion, with hyperplasia of the gland-cells, and an enormous multiplication of plague bacilli.

Symptoms. *Incubation period.*—Symptoms of plague begin to show themselves after an incubation period of from 2–8, rarely 15 days.

The average case of plague: prodromal stage.—In a certain but small proportion of cases there is a prodromal stage characterized by physical and mental depression, anorexia, aching of the limbs, feelings of chilliness, giddiness, palpitations, and sometimes dull pains in the groin at the seat of the future bubo.

Pestis minor, or ambulatory stage.—Abortive or ambulatory cases of bubonic plague have been reported in connection with almost every true outbreak of the disease, and in some constitute a high proportion.

Joltrain reported several of these cases in the Paris outbreak of 1920 and also in Algeria ; Leger described similar cases in Dakar, and Fonquernie in Madagascar. Clinically these cases present mild, general febrile symptoms with a bubo, and when that suppurates the temperature falls and the patient recovers. The diagnosis may be difficult because the plague bacillus may be very scanty in the pus. The differential diagnosis has to be made from climatic bubo (*Lymphogranuloma inguinale*).

From the clinical aspect, plague in man can be divided into the following varieties :— (1) Bubonic (2) Septicæmic (3) Pneumonic and (4) Meningeal.

Bubonic plague.—This is the most common form and constitutes about three-quarters of the total number. The incubation period is usually very short ; generally within twenty-four hours the characteristic bubo, or buboes, develop. Generally (in 70 per cent.) the bubo appears in the groin, especially on the right side and affecting one or more of the femoral glands ; less frequently (20 per cent.) the axillary ; more rarely still (10 per cent., especially seen in children) the submaxillary lymphatic glands may be the seat of the bubo, and the tonsil may be the primary focus of infection. In rare instances cervical buboes may actually result. Buboes are usually single, but in about one-eight of the cases they form simultaneously on both sides of the body. Very rarely buboes form in the popliteal, epitrochlear, or clavicular glands. Occasionally they develop simultaneously in different parts of the body. A curious point noted in North West America is that in squirrel-conveyed plague axillary buboes are common. Plague buboes vary very much in size. Sometimes they are not as large as a walnut ; in others again they may be as large as a goose's egg. Pain may be very severe, but sometimes it is hardly felt. Besides the enlargement of the gland there is, in most instances, considerable pericellular infiltration and œdema.

Stage of fever.—The stage of invasion may last for a day or two without serious pyrexia, but usually it is much shorter, or it may be altogether absent. The disease usually develops abruptly, without a definite rigor or other warning, the thermometer rising rapidly to 103° or 104°, or even to 107° F., with corresponding acceleration of temperature and pulse. The temperature usually falls after three or four days and then rises again. The skin is now dry and burning, with bloated face ; the eyes congested, sunken and staring ; hearing is dulled. The tongue is swollen, covered with thick creamy fur, which dries rapidly and soon becomes brown or almost black. Sordes form on the teeth and about the lips and nostrils. Thirst is intense ; prostration extreme, whilst from utter debility the voice is reduced to a whisper. Sometimes there is wildly fatuous delirium, or it may be of the low muttering type.

Coma, convulsions—sometimes tetanic—retention of urine, subsultus tendinum and other nervous phenomena ensue. Vomiting is in certain cases very frequent. Some patients are constipated, but in others there is diarrhœa. The spleen and liver are usually enlarged. Urine is scanty, but rarely contains more than a trace of albumin. The pulse, at first full and bounding, in the majority rapidly loses tone, becoming small, frequent, fluttering, dicrotic and intermittent. In the later stages the heart is usually dilated, the first sound being feeble or absent altogether.

Hæmorrhages are seen on the mucuous membranes in severe cases. There is usually a polymorphonuclear leucocytosis.

Stage of recovery.—In favourable cases, sooner or later, after or without the appearance of the bubo, the constitutional symptoms abate with the setting in of profuse perspiration. The tongue begins to moisten, the pulse-rate and temperature to fall, and the delirium to abate. The bubo, however, continues to enlarge and to soften. After a few days, if not incised, it bursts and discharges pus and sloughs—sometimes very ill-smelling. In rare instances suppuration is delayed for weeks ; whilst in some the bubo subsides after a few weeks, or perhaps months, without having broken down. The sores left by the buboes and abscesses of plague are extremely indolent and may take months to heal. Owing to contracture and fibrosis of lymphatic tissue, œdema of the leg on the affected side usually supervenes. Convalescence sets in some time between the sixth and tenth day, although it may be delayed for a fortnight or three weeks.

Skin affections.—In a very small proportion of cases what are usually described as carbuncles, which are in reality small patches of moist gangrenous skin that may gradually involve a large area, develop on different parts of the integument. These occur either in the early stage or late. Sometimes they slough and lead to extensive gangrene.

Kirk and Crawford have described a generalized papular rash on the hands, feet and pectoral region. Should life be continued sufficiently long, the vesicles become converted into pustules resembling smallpox. These observations confirm in a remarkable manner, as MacArthur has pointed out, the old writers who described manifestations, in the Plague of London of 1665, as " blains."

Complications.—Occasionally a pyæmic condition, with boils, abscesses, cellulitis, parotitis, or secondary adenitis, succeeds the primary fever. During convalescence tragic sudden cardiac failure is not uncommon. Secondary pneumonic plague with blood-stained sputum may supervene, but the patient may recover.

Hæmorrhages of different kinds are not an unusual feature of plague—ecchymotic effusions of a purplish or dull-red tint, varying in size from a hemp-seed to half an inch in diameter. These are found frequently in certain malignant epidemics.

Abortion almost invariably occurs in pregnant women ; the fœtus sometimes shows signs of the disease.

Death may take place at any time. Usually it occurs between the third and fifth day, with symptoms of profound adynamia, heart-failure, or perhaps from convulsions, from coma, from internal hæmorrhage or, later, from exhaustion consequent upon prolonged fever or suppuration, or from secondary hæmorrhages.

Septicæmic plague, or pestis siderans.—In this type there is no special enlargement of the lymphatic glands during life, although after death throughout the body they are somewhat enlarged and congested. The high degree of virulence and the rapid course of the disease depend on the entry of large numbers of the bacilli into the blood, where they can be readily found during life. The patient is prostrated from the outset ; he is pale and apathetic; there is generally little febrile reaction (100° F.). Great weakness, delirium, picking of the bed-clothes, stupor and coma end in death on the first, second, or third day, or, it may be, later. Frequently in these cases there are hæmorrhages.

It is probable that in many cases of bubonic plague there is some degree of septicæmia, and that in a minority of cases this may progress to the full septicæmic type, or may give rise to plague pneumonia.

Pneumonic plague.—This occurs frequently in epidemic form among the marmot-trappers of Northern China, who live under very insanitary conditions, but may occur spontaneously wherever the bubonic form is found. It is especially dangerous to the patients, attendants, and visitors, because of the multitude of bacilli which are scattered about in the patient's expectoration, and because the clinical symptoms are unlike those of typical plague and are apt to be mistaken for some ordinary form of lung disease. The illness commences with rigor, malaise, intense headache, vomiting, general pains, fever, and intense prostration. In the early stages there may be little to suggest pneumonic plague, except the marked discrepancy between the almost negligible physical signs and the gravity of the patient's condition. Cough and dyspnœa set in, accompanied by a profuse, watery, blood-tinged sputum. The sputum is not viscid and rusty, as in ordinary pneumonia. From the outset clouding of consciousness is very marked. Moist râles are audible at the bases of the lungs, the breathing becomes hurried, other symptoms rapidly become worse, delirium sets in, and the patient usually dies on the fourth or fifth day. This is the most fatal as well as the most directly infectious form of plague. A single authentic recovery has recently been reported from South Africa (Clark and Goldberg, 1943). Epidemicsof 50,000 and more cases have occurred in Manchuria, where the plague bacillus exists as an intestinal infection in the marmot, which acts as a reservoir of the virus. Pneumonic plague has been recorded from Nigeria, the Gold Coast, Ecuador, New Orleans and elsewhere. In these countries hæmorrhage into the intestinal canal occurs in about 8 per cent. of plague-infected rats and the organism is passed out in the fæces; in this manner the plague bacillus can be disseminated in dust and inspired by man directly into the lungs. (Connal and Paisley.) Murdock believes that secondary plague pneumonia occurs in a proportion of patients with bubonic plague and that the disease is then spread by droplet infection and inhalation. Pneumonic plague is exceedingly dangerous to nurses and others in contact with the patients.

It has been pointed out by Kellog that, whereas in rat-borne plague pneumonia is rare, in squirrel plague it is the reverse.

Meningeal plague.—Chronic relapsing meningeal plague was described by Meyer and colleagues in California (1937). Signs and symptoms of meningo-encephalitis were exhibited with high pyrexia. *P. pestis* was isolated from the blood and cerebrospinal fluid. Previously, meningitic involvement was recorded between the tenth and twentieth days in patients who survived as long as that.

Relapses.—Relapses have been recorded in bubonic plague and are specially dangerous.

Mortality.—The case-mortality of bubonic plague varies in different epidemics. It is usually greatest at the beginning and height of the epidemic. The death-rate may be anything from 60 to 95 per cent. of those attacked. Much appears to depend on the social condition of the patient and the attention and nursing available. Thus, in a Hong Kong epidemic, while the case-mortality among the indifferently fed, overcrowded, unwashed, and almost unnursed Chinese amounted to 93·4 per cent., it was only 77 per cent. among the Indians, 60 per cent. among the Japanese, and 18·2 per cent. among the Europeans—a gradation in general correspondence with the social and hygienic conditions of the different nationalities. In the South American epidemics and in the recent circumscribed epidemics in Europe the mortality was only about one-third of that in India and China. Pneumonic plague is generally fatal in from three to four days. Van den Berg and Vos report that in an epidemic in Java (1930) in 66 cases of plague the mortality was 76 per cent. The sixteen who recovered had all been suffering from bubonic plague. The chances of recovery were somewhat better in men than in women. In this series there were 57 cases of bubonic plague, two of plague ulcers, 29 of septicæmic plague, and one of primary plague pneumonia.

Diagnosis.—Fever and adenitis during a plague epidemic must invariably be viewed with suspicion, and particularly if the fever rapidly assumes an adynamic character. In the early stages diagnosis may be very doubtful, especially in pneumonic plague, and in the countries of high filarial endemicity in which filarial adenitis is common. Blood-culture was recommended by Onoto, by inoculating blood into broth containing 1 per cent. of sodium citrate. Rosier stated that in Java splenic puncture is valuable in establishing a diagnosis and is not opposed by the native population. Junior and de Albuquerque described an allergic skin test for which an emulsion of infected guinea-pig lymph gland is used. In Western America the differentiation of mild cases of plague from tularæmia is important (p. 281). The discovery of the bacillus in the glands, blood, sputum, or discharges is the only thoroughly reliable test. Should a cocco-bacillus be found with the characteristic bipolar staining, it should be cultivated by Haffkine's method in broth on which clarified butter (ghee) or coco-nut oil is floated (*see* p. 255). In case of doubt, animal inoculation should be used ; a little of the virus from the patient or a culture is rubbed into a shaven area (1 in. square) on the abdomen of a white rat or a guinea-pig. *P. pestis* inoculated in this way kills the guinea-pig in seven days, the rat sooner, and white mice in forty-eight hours. The latter may be inoculated at the root of the tail.

Post-mortem indications of plague in the rat.—Before rats suspected of being plague-infected are handled, they should be immersed in disinfectant to destroy ectoparasites.

The lymphatic glands should be first exposed. If the rat is infected, subcutaneous injection around the glands is generally recognizable. If the gland is itself inflamed, this is almost diagnostic of plague ; the liver will be yellow, sprinkled with innumerable pinky-white granules. The spleen is enlarged, congested, and occasionally granular. The serous membranes are of dull lustre with petechial or diffuse hæmorrhages. Serous or blood-stained serous effusions are present in 72 per cent. of such rats; if, on microscopical examination of scrapings from glands or spleen, bipolar-staining bacilli are detected, the case is probably plague. Too great stress must not be laid on bipolar staining alone, as this feature depends somewhat on the method; it is best demonstrated by the Leishman eosinazur stain. *P. pestis* persists for a long period in the bone marrow of plague rats, even after putrefaction has set in.

P. pestis, *P. pseudotuberculosis rodentium* and *P. aviseptica* closely resemble each other and are scarcely distinguishable by the usual cultural methods, but the latter two have no "envelope substance," though they have a common antigen with *P. pestis*. None coagulates milk, but in agar *P. pestis* produces a more glistening membranous growth. *P. pseudotuberculosis rodentium* produces a clear, yellowish growth on potato. On Drigalski medium it produces blue colonies, and *P. pestis* reddish ones. *P. pseudotuberculosis* readily associates itself with the production of smooth and rough colonies with all degree of transitions between them. The smooth colonies show closest association to *P. pestis* and are the most virulent. *P. aviseptica* produces indol and does not reduce methyl red.

The most satisfactory means of differentiation is animal inoculation. Rabbits, guinea-pigs, and white mice are susceptible to *B. pseudotuberculosis*, but white rats are not. The Indian Plague Commission laid stress on the latter point, as these animals are instantly killed by *P. pestis*. These organisms belong to the hæmorrhagic septicæmia group.

Rodent plague and fleas.—In the investigation of rodent plague the inoculation into animals of pooled fleas is important. Cyanide gas is the best method of collecting fleas from rodents. The long bones of rodents may be sent to the laboratory for culture tests of marrow.

Differential diagnosis.—Bubonic plague has sometimes to be distinguished from other affections associated with enlarged glands, such as streptococcal infections, *lymphogranuloma inguinale*, filarial adenitis, and occasionally from an anthrax pustule.

In filarial and streptococcal infections lymphangitis tracks are usually visible, but in bubonic plague there is usually no visible sign of the primary infection. In glandular fever the cervical glands are as a rule primarily affected and there is an excess of heterophil antibodies in the serum (goat's corpuscle test).

Generalized pustular plague has to be differentiated from chickenpox or smallpox; carbuncular plague may be mistaken for anthrax; and septicæmic plague may be confused with typhus and subtertian malaria. In the United States, North Europe and Russia, tularæmia may resemble plague.

Pneumonic plague differs from other forms of pneumonia in three main characteristics: (1) The patient is extremely prostrated, although his critical state can hardly be accounted for by such physical signs as are present in the chest; but by the time definite involvement of the lung can be demonstrated, he generally dies. (2) The sputum is watery, never thick, and soon becomes very blood-stained. (3) Pleural effusion is usually present in plague pneumonia.

Treatment.—The treatment of plague is mainly symptomatic. The asthenic tendencies of the disease must ever be borne in mind, and depressant remedies of all kinds carefully avoided.

During the earlier stages, when headache and perhaps high fever are urgent, much relief may be obtained from ice-bags to the head and neck. If it be deemed advisable to attempt to lower the temperature, sponging the body every hour with warm water is a much safer measure than antipyrin and similar drugs. Vomiting is usually relieved by a full dose of calomel followed by a saline. If not, or if diarrhœa be present, Lowson recommended ice pills and an effervescing mixture containing morphia and hydrocyanic acid. Sinapisms to the epigastrium are useful. In collapse, stimulants of various kinds, including strong ammonia to the nostrils, and ether hypodermically, are indicated ; they sometimes succeed in resuscitating a sinking patient. Given with judgment, morphia is by far the best hypnotic. Hyoscine ($\frac{1}{200}$ to $\frac{1}{75}$ gr.) or chloral (20 gr.) and bromide of potassium (30 gr.) are of service for the same purpose. Diarrhœa, if urgent, is best treated by intestinal antiseptics, such as salol, in 10-gr. doses every four hours.

The buboes in the early stage may be treated with applications of glycerin and belladonna. Should they become red and inflamed, they must be poulticed and, when they soften, incised and dressed with iodoform. Indolent bubonic swellings should be treated with iodine liniment. The injection directly into the buboes of iodine and a solution of camphor and thymol mixed in equal parts, in doses of ½ to 1 c.c., according to the age of the patient, has been advocated. Intravenous injections of iodine have gained a certain reputation. A 1 per cent. solution with double the amount of potassium iodide is advised in doses of 5 to 10 c.c. daily for four days.

Serum-therapy.—Yersin, Calmette, and Borrel immunized a horse by intravenous injections of living virulent cultures and produced an effective antiserum. In septicæmic plague it must be given intravenously in large doses (100–250 c.c.), and frequently repeated, but, to be effective, must be administered early in the course of the disease. Anti-plague serum has been tried in India, and Dawson reported that in bubonic plague, in doses of 30-40 c.c., the results have been encouraging. Injections in and around the bubo were advocated by Bonebakker. E.V., an avirulent strain of *P. pestis*, is used for producing this serum.

Sulphonamides.—Durand, Girard, Schütze and others showed that certain sulphonamides, especially sulphapyridine, protect mice infected with plague, if combined with anti-plague serum. According to Sokhey and Dikshit, sulphathiazole has shown itself superior to sulphapyridine in the treatment of human plague. Kamal found a combination of serum with sulphapyridine best in the treatment of the bubonic form. Wagle and his colleagues published a report on 237 patients, of whom those treated with sulphathiazole showed a significant reduction in mortality as compared with those treated by other methods.

General prophylaxis.—The prophylaxis of plague, as of other infectious diseases, has to be considered from the standpoint of the community and also from that of the individual. It includes measures for preventing the introduction of *P. pestis*, for staying its spread if introduced, and for securing its destruction.

Quarantine.—Modern systems of land or sea quarantine directed against plague take cognizance of the facts that the incubation period of the disease may extend to ten days, and that plague may affect certain of the lower animals as well as man. Ten days is the minimum period that should elapse from the time of departure from an infected place, the date of the last death, or the arrival of a ship or batch of travellers with cases of plague among them, before granting free pratique.

The eradication of rats from ships requires special measures. Sulphur dioxide may be used in concentration of 2 per cent., either as 8 lb. of roll sulphur or 4 lb. of liquid sulphur dioxide per 1,000 cubic feet. In the Clayton system, which has never been extensively used in British ports, sulphur is burned in a furnace and the gas propelled by fans throughout the ships.

Hydrogen cyanide is being more extensively employed. Under proper supervision it is comparatively safe and has decided advantages over sulphur, as it does not tarnish metals or damage articles. Hydrogen cyanide diffuses slowly. Small amounts which may be absorbed are rapidly evolved and oxidised on exposure to air or during cooking. Hydrogen cyanide may be generated either by pumping liquid HCN from cylinders or by throwing glass ampoules into holds, or from outside by the Glen Liston apparatus. "Discoids," wood pulp discs saturated with ¼ oz. HCN, may be used. Calcium cyanide dust (known in the trade as Calcid or Cyanogas) in a dusting apparatus will dislodge rats from deck fittings and lifeboats, or may be blown as a fine powder through a rubber tube behind panellings.

The proprietary article "Zyklon" consists of highly absorbent material saturated with lachrymatory gas. It is supplied in hermetically-sealed tins and after fumigation may be disposed of as refuse.

The Nocht-Giemsa method of fumigation consists of a mixture of carbon monoxide and carbon dioxide generated from incandescent coke driven into the ship.

For fumigation the ship is divided into sections each of which is measured by volume. Water-bottles and cabin water-tanks are emptied, moist food removed and mattresses turned on edge. All apertures are sealed. Danger boards are prominently displayed. Ships may be fumigated loaded or unloaded. A plague infected ship should be treated before unloading.

When plague breaks out in a small village community, as soon as the disease is recognized, measures should be taken to prevent the inhabitants leaving the locality and thus disseminating it. There is little danger of this until the inhabitants become alarmed by a rapid extension of the disease. If possible, after the patients have been isolated in a special hospital, the village should be evacuated for a month. The safest and most thorough form of disinfection is by fire, and in an isolated village prompt burning of the infected houses is the surest method of stamping out the infection. The clothes and bedding of all patients should be burned. The dead should, with as little delay as possible, be buried in deep graves or cremated. Isolated observation camps should be organized, in which "suspects" and "contacts" may be segregated for a time equal at least to the incubation period of the disease. War should be waged against all rats and mice, and their corpses burned. This is specially important in rat-infested quarters of Eastern towns, bazaars, grain stores, go-downs, etc.

In an outbreak in a town, it must be borne in mind that plague, once established in human beings, is communicable to others and to rats by the expectoration, and by discharges from the buboes or glandular swellings; and that a plague in rats usually precedes plague in human beings. The main efforts should be directed towards destruction of rats by methods detailed on pp. 275-276. In addition, therefore, to prompt notification of plague patients, a system designed to obtain information on plague in rats should be instituted. Every rat destroyed must be bacteriologically examined.

After death the rat is treated with Flit or soaked in lysol. Smears are made from lymph glands, liver and spleen, and stained by Leishman. Broquet's medium (calcium carbonate 2; glycerine 20; distilled water 80 parts) is a good preservative for fleas and permits isolation of *P. pestis* after six days.

For the detection of plague-infected houses, guinea-pigs, which do not harbour fleas as a rule, are turned loose in warehouses as convenient traps for rat-fleas.

In India the compulsory inspection of all dead bodies before burial has been found a valuable measure for discovering infected houses and localities.

Destruction of vermin and other measures in anticipation of the introduction of plague virus.—The campaign against rats is usually carried on by rat-traps and rat-catchers, and the cautious laying down of poisons such as arsenic, phosphorus, and baryta. As no one method is satisfactory, it is usual to employ several at the same time. The pumping of SO_2 gas under pressure is useful for warehouses. So long as the sulphurous-acid gas is dry and not used on damp articles, no damage is done to merchandise. Care has to be taken with damp things, as they may get discoloured.

Where possible, houses and warehouses should be made rat-proof—not an easy measure, considering the burrowing and climbing habits of the rat. *Rattus norvegicus* can penetrate ordinary lime-mortar or soft brick, but is stopped by cement and concrete. Its burrows may attain a depth of 18 in., but *Rattus rattus* is not so active in this respect. Simpson recommended that walls should be at least 6 in. thick when made of hard brick or concrete, and that they should extend to not less than 18 in. below the level of the ground floor, and the latter should be paved with concrete 8 in. thick, covered with ½ in. of cement. All ventilators should be protected with iron gratings, and all openings around wires and pipes cemented. In New Orleans some warehouses are elevated, leaving a clear open space beneath: in others an impervious wall is built around the ground floor, penetrating 2 ft. into the ground. In a third, and a most effective type, the ground floor is laid out in concrete with a protective wall round the edges sinking 2 ft. into the ground. The mooring cables of ships should be shielded in such a way as to prevent egress or ingress of rats, and all gangways should be taken up at night or when not in use. Native food-stores are, as a rule, set out on poles and can be protected from rat-invasion by suitable wooden discs. Sprinkling chloride of lime in the vicinity of the burrows has a deterrent effect. House improvement as an antiplague measure has been officially adopted by the government in Java since 1914 and, though costly to begin with, has proved economical in the long run. In some districts the principle of voluntary house improvement was adopted. No compulsion was exercised, other than official propaganda. The result is claimed as a complete success. Plague has disappeared and the population is contented. Compulsory inspection, condemnation of houses, spleen puncture after death in suspected cases and isolation of contacts are unpopular measures.

In South Africa rigorous measures have been adopted by the Health Department to prevent the spread of rodent plague; it has endeavoured, apparently with success, to place a gerbille-free belt between the mountain range and the sea. Gangs, working under departmental rodent officers, employ two main methods—poisoning and gassing. The poisoning is effected by dropping strychnine-impregnated grain into gerbille burrows. Near homesteads, a Capex cartridge is lighted, plunged into a burrow and the opening closed with earth. Meyer has shown that methyl bromide, sprayed at the rate of 10 c.c. per burrow-opening, is efficient in controlling burrowing rodents and their fleas. Care, however, must be taken in its application.

Prophylactic measures based on a consideration of the flea fauna.—Should further research prove the inability of *Xenopsylla astia* to transmit plague, it should be possible to divide a country into potential and non-potential plague zones by a survey of the rat-flea population. The energies of the Sanitary Department can by these means be focused on the danger spots.

Personal prophylaxis.—All unnecessary visits, either to plague patients or plague neighbourhoods, should be, if possible, prevented Attendants on the sick ought to take care that the ventilation of the sick-room is thorough, that cubic space is abundant, and that the utmost cleanliness is practised. Nurses must not hang over patients unnecessarily; they must also be careful to seal up and cover any wounds, no matter how trifling, on their own hands. Stools and urine must be disinfected, and hands frequently washed. To obviate risk from wounds and to prevent the access of fleas, those engaged on plague duties should wear boots and have the legs protected by trousers tied tightly round the ankles or, better, by puttees. Leather gloves are advisable if there is much handling of furniture or of anything likely to abrade the skin. In the interests of public health it is imperative to isolate all cases of bubonic and septicæmic plague and their contacts.

The attendants on pneumonic cases should provide themselves with masks of muslin, three- or four-fold, changed when at all damp, and also with goggles to protect the eyes. In Mukden a mask of absorbent cotton-wool (16 by 12 cm.) enclosed in muslin, and retained in position by a many-tailed gauze bandage, together with goggles, rubber gloves, and cotton uniform, proved thoroughly effective. Evacuation of the people from insanitary and overcrowded dwellings and their installation in camps where better hygienic conditions can be arranged is imperative. Churches, schools and theatres must be closed. Cordons within the affected area, to limit the infection to a circumscribed portion, may assist. In pneumonic plague epidemics general inoculation with plague vaccine is advisable.

Prophylactic inoculation. *Haffkine's inoculations.*—Early during the Bombay epidemic Haffkine introduced a system of prophylactic inoculation which is of proved value, both in reducing the number attacked with plague from 77 to 85 per cent., and in diminishing by 80 per cent. the mortality in those attacked. It consists essentially in the subcutaneous injection of six-weeks'-old cultures of plague bacilli incubated at 25–30° C. and killed by heat—65° C. for one hour; carbolic acid 0·5 per cent. is then added; up to 4 c.c. is injected according to the size and age of the individual. The Indian Plague Commission reported strongly in favour of these inoculations, which furnish a protection that lasts about twenty months. Glen Liston stated that in the inoculated the incidence of plague was 8 per 1,000 of the population concerned, whereas it was 34 per 1,000 in the uninoculated in the same communities; the case-mortality in the inoculated was 39·5 per 100 attacked; in the uninoculated 78 per 100. The best results are obtained from a two-months' growth of *P. pestis* has been stored about eighteen months. It needs great care in its preparation. Its storage in hermetically sealed bottles should be insisted upon, and every bottle ought to be tested before use. The resulting reaction is sometimes severe. The efficacy of the vaccine depends upon the virulence of the bacilli composing it; cultures made from non-virulent strains are useless. The potency of plague vaccine is enhanced by the incubation of plague cultures at 37° C. in place of 26° C.

So far, Haffkine's prophylactic is the one most frequently used and gives the best results. In 1927, 90,000 inoculations with plague vaccine prepared at the Entebbe laboratories were administered in Uganda. As an index of its efficacy it was noted that amongst 232 cases subsequently attacked by plague the recovery-rate was 40 per cent.

Those in attendance on plague patients should receive 20 c.c. of Yersin's anti-plague serum, and 3 c.c. of Haffkine's vaccine on the same day; ten days later a second dose of vaccine should be given. Attendants should wear lysol-impregnated gowns fastened at the wrist, ankles and neck, rubber gloves and gum-boots. They should not shave, but they should disinfect themselves and their clothes daily.

Prophylactic inoculation with *avirulent living plague bacilli* was practised in Java by de Vogel and Otten. The smooth variety on culture has been used as antigen, and 400,000 persons were immunized in this manner without incident or accident. The plague strain "tjiwidej" was discovered by accident, and is so avirulent that both rat and guinea-pig can withstand a whole culture when inoculated. The animal experiments shew much better immunity with this living vaccine than that obtained with dead cultures. Otten's method was commenced in 1935 and up to 1939 total injections numbered 9,286,287. Excellent results have been obtained and the present decline in the epidemic is attributed chiefly to this vaccine. The mortality in the vaccinated fell to about 20 per cent. Girard reported upon similar results obtained with his living vaccine in Madagascar. Passa recorded that in that island cases of plague fell from 3493 in 1935 to 918 in 1937. Van Hoof used this method extensively in the Belgian Congo.

An oral plague vaccine (*Pestedo*) has been prepared by Poulenc Frères and is well taken by natives who object to inoculation, but the results are unsatisfactory.

DESCRIPTION OF THE COMMONER SPECIES OF RATS CONCERNED IN THE SPREAD OF PLAGUE

The spread of plague and epizoötics amongst rats seems to be primarily by the fierce *R. norvegicus*. The more delicate *R. rattus* receives its infection from the former, the sewer rat. Both these species are pestigenic. When the rat dies the fleas desert the body and seek a new host; thus if a sewer rat (*R. norvegicus*) dies in the basement, the fleas attach themselves to the black house rat (*R. rattus*), and are spread to human beings.

Terms employed.—Rodents which are capable of being infected with plague are divided into *pestiferous* and *pestigenic*; thus the common mouse is a pestifer, but is not ordinarily a transmitter. *Selvatic* (or *sylvatic*) plague is the plague of the hinterland. In North Africa, for instance, plague of the "bled" of Tunisia has been regarded as selvatic and due to desert rodents; further south in the Sahara a mouse (*Psammomys roudairei*), though predominant and a very susceptible animal, has hitherto not been affected.

An intimate knowledge of the appearance and habits of the many species of rats is hardly necessary to the tropical specialist: considering the important rôle several species play in the spread of plague he should, however, be able to identify the more domestic varieties. For this purpose the following Table, contributed by M. A. C. Hinton, will be found useful:

Rattus rattus, Linn.—The black rat. Build slender; muzzle sharp; ears large, translucent, cover eyes when folded down; tail usually long, never much shorter than head and body; coarse hair on rump; hind foot (heel to tip of longest toe, without claw) 35–40 mm.; weight of adults rarely more than 8 oz. Indigenous, wild, more or less arboreal in Indo-Burmese countries. In tropics generally dominant domestic rat in houses and ships. The chief domestic races are distinguished as follows:

A. Back reddish or greyish-brown.
  a. Under parts pure white or pale lemon. *R. r. frugivorus* Raf. (= *tectorum*). Common in Mediterranean region. *R. r. kijabius.* Uganda.
  b. Under parts darkened.
    *a*¹. Ventral hairs with rusty tips. *R. r. rufescens* Gray. Common rat of Indian houses.
    *b*¹. Ventral hairs without rusty tips. *R. r. alexandrinus* Geoff.
B. Back black; under parts dusky or slate-grey. *R. r. rattus* Linn. Essentially a domestic form which has been evolved in cold temperate countries.

N.B.—The black rat tends to be brown in the tropics.

The forms *frugivorus*, *alexandrinus*, and *rattus* have now acquired an almost world-wide distribution; *frugivorus* is the least, *rattus* the most modified race. These are climbing rats, common on ships; frequent in dwellings in warm countries, and not shunning man; they are of especial importance as plague-carriers; attain sexual maturity early (min. weight sex-mature = 70 grm.); breed throughout the year; gestation about 21 days, but with concurrent lactation about 31 days; litter of from 4 to 11; average litter 5 or 6.

Rattus norvegicus, Berkenhout (=decumanus).—The brown, grey or sewer rat. Robust; muzzle blunt; ears small, opaque; tail noticeably shorter than head and body; fine hairs on rump; hind foot 40 to 45 mm.; weight of adults commonly 17 oz., often much more; colour brown or grey above, silvery below. A melanic form (often confused with *R. rattus*) quite common.

RAT DESTRUCTION (DERATIZATION)

Terriers may be used, the rats being driven out of their holes by flooding from a watercart. Cats are useful, but they are susceptible to plague. Traps of all description are of value, and rats readily enter a funnel-shaped trap showing a light at the far end. Runs may be made with double closing doors, or gins or nipper traps may be placed in the path of rat-runs. One man can attend to 100 to 200 traps a day. In towns and ports where plague exists, 40 to 50 traps should be set per day per 1,000 inhabitants. Rats which are caught alive must be asphyxiated and then combed for fleas. The flea is placed for twenty-four hours in pure phenol to make it transparent, so that species and sex may be determined. The total number of fleas divided by the number of rats gives the "flea-index."

One of the modern methods of rat destruction is the use of lithographic varnish or "ratsticker." The varnish is spread on a board in a place frequented by rats, with a piece of cheese or other material as a bait. On coming into contact with this substance, the rat becomes hopelessly entangled and its squeals attract other rodents to the rescue, so that they in turn become trapped. Rat traps should not be handled, except with gloves. They may be covered with mud or anointed with oil of aniseed, which removes the human smell.

Baits.—A good bait is one which differs from food usually found on the premises. In fish shops, meat, cheese or bread should be used. In grain stores, bloaters, cheese, etc. Dry bread is always acceptable, while oatmeal and tallow can also be used. It is said in the tropics that tomato is specially tempting.

Poisons.—*Squill* (*red squill*) pancakes are made with beef dripping to which has been added 20 per cent. of finely chopped *Urginea maritima* (red variety). The pancakes are cut into baits each ½-inch square. Various squill preparations are on the market. Squill is mixed with equal parts of milk, and 8 lb. of bread, soaked, for every gallon of solution. The toxic dose for a rat is 1·3 c.c. of a liquid extract. Its action on the rat is slow; the first symptoms being excessive purging, thirst, and general discomfort, followed by paralysis and convulsions. Death is hastened by drinking. The ground-up bulbs make the best bait. On the basis that a rat eats one-tenth of its body-weight every 24 hours, each bait should consist of 60 gr. In autumn female rats are especially attracted by these methods. Powdered squill is quite dangerous to handle, and liquid extract is the safest preparation.

Barium carbonate, 1–2 gr. kills a rat. Cats and chickens can stand 10–15 gr., whilst dogs can take 100 gr. This poison drives rats to seek water so that they die in the open. A 10–50 per cent. mixture of barium carbonate with fatty basis (*i.e.* tallow) forms one of the safest and most effective rat poisons. "Zelio" paste, or poisoned grain (Bayer), in which the grain is thoroughly soaked, is said to be absolutely tasteless and readily eaten by rats. The bait is set at night and removed in the morning. After touching the poisoned bait the hands should be washed.

Effective, but dangerous to stock.—(*a*) Strychnine and barium—Battle's vermin killer. (*b*) Arsenic and barium—"Rough on Rats." (*c*) Phosphorus— "Extermo," "Rodine," "Farmer's paste," "Roth's paste" and "Sandford's paste." In Hawaii a banana-phosphorus bait is said to be effective. Cyanide preparations are better than trapping or baiting, because they also destroy fleas.

Partly effective but dangerous to man.—The virus of Danysz and similar viruses, which are bacillary in origin, vary very much in lethal effects and have been known to cause "choleraic" symptoms in man. In the tropics they require frequent subculture.

Cultures.—Danysz virus and other bacilli have been used with the object of causing epizoötics in these rodents, but they have not been successful on the whole. In South Africa similar attempts have been made to extirpate gerbilles by an organism known as the Tiger River disease (*B. monocytogenes*) (E. G. Murray), and this has been partially successful.

Various poisons for use in selected cases.—(*a*) Arsenic, 20 per cent. with meal. (*b*) Dish of oatmeal mixed with sugar, grated Parmesan cheese, and a small quantity of strychnine. (*c*) Dish of chicken heads. A pinch of strychnine should be placed in each neck with a drop of blood.

FLEAS

The natural history and classification of these insects are found on p. 994.

CHAPTER XII

TULARÆMIA

Synonyms. Deer-fly Fever; Pahvant Valley Plague; Rabbit Fever; Ohara's Disease.

Definition.—Tularæmia is a specific infectious disease of rodents, caused by *Bacterium* (*Pasteurella*) *tularense*, and is transmitted from these animals to man by the bite of infected blood-sucking insects, or by the handling or dissection of infected jack-rabbits and other rodents. From group agglutination tests it appears that *B. tularense* is closely allied to the *Brucella* group, but has epidemiological relationship to plague, as both are primarily diseases of rodents conveyed to man by biting insects.

History and geographical distribution.—*B. tularense* was discovered by McCoy and Chapin in 1911 in a plague-like disease of rodents, more especially the ground-squirrels, of California. In 1914 Vail recognized ocular tularæmia in the United States, and in this case Wherry and Lamb were able, for the first time, to isolate the *Bact. tularense* from man. The disease is more or less confined to the States of California, Indiana, Kentucky, Ohio, and Utah, in the United States. Although first found in Tulare County, California, by 1928, 650 cases had been reported in all States in the Union, with the exception of Wisconsin, Washington and the New England States. In Russia, the disease has been recognized in native hunters of the musk-rat and the water rat, which are killed for their fur, and the Russian observers have noted that the infection is widespread amongst rodents in places where no examples of the human disease have been identified. There is some evidence that it existed in Astrakan as early as 1877. Occasionally it may occur amongst sheep, especially in Alberta, Canada. The disease has been recognized in Norway, whilst Olin and Sehlstedt found cases in Sweden, as far north as latitude 66° N. The source of infection is the arctic hare, and *Chrysops discalis* is the transmitter. Diseased squirrels may also be responsible. Tularæmia has now been recorded in Germany (1931, 1933 and 1936), Lower Austria (1925 and again in 1936), Czechoslovakia (1936), and Moravia, as well as in Turkey in Europe (1936), in Asia Minor and Japan. In South Moravia, thirty to forty-five days before the notification of human cases, a great mortality was reported among field voles and hares.

Epidemiology and endemiology.—In American endemic areas the disease is most prevalent in the months of June, July, and August, when it is conveyed by a blood-sucking fly, *Chrysops discalis*, from one infected jack-rabbit to another. In Scandinavia and in Northern Europe most cases occur from July to October; in Southern Europe and Asia Minor from June to August. Tularæmia is a disease of the rural population, particularly field workers, but it has also been recorded among dealers in rabbits who handle infected jack-rabbits, and those who prepare their skins for market. In 1924 Parker and Spencer found that the tick (*Dermacentor andersoni*) could act as a host and as vector of the disease in man and in rodents, and demonstrated that hereditary transmission takes place in it. They further showed that the rabbit tick (*Hæmaphysalis leporis-palustris*) acted as a vector from one rodent to another. Olin studied a serious outbreak of 115 cases in Sweden in 1937 which occurred especially among peasant women, who in summer-time go bare-footed and who are stung by numerous mosquitoes, and he considered that these insects may act as vectors. Although in the main an insect-borne disease, it may be water-borne. "Lemming fever" in Norway is tularæmia due to drinking water polluted by bodies and excreta of lemmings. In Montana, U.S.A., streams are similarly contaminated by beavers, and in Wyoming these animals have been found dead in large numbers from *B. tularense* infection. Ingestion tularæmia is contracted by eating insufficiently cooked flesh of an infected animal.

Ætiology.—*B.* (*Pasturella*) *tularense* is a small non-motile, Gram-negative organism, measuring 0·3–0·7 μ in length ; when stained in the tissues it gives the appearance of being surrounded by a capsule. Though normally occurring as a rod-like structure, it frequently assumes a coccus shape. It stains best in tissue preparations with Giemsa's stain, but in smears from cultures it shows up well with aniline gentian-violet. On account of their small size, some of the organisms pass through the coarser bacterial filters.

The organism is difficult to cultivate ; it will not grow on plain agar or in bouillon, and, until recently, had been cultivated only upon the coagulated yolk of hen's eggs, but Francis succeeded in producing an abundant growth upon serum-glucose-cystine agar. The cystine medium is inoculated with the heart's-blood of the infected animal, or a small piece of the liver or spleen is rubbed on the surface and allowed to remain in contact with the medium. Growth appears about the third day, and flourishes luxuriantly on subcultures without the addition of fresh animal tissue. To ensure the primary growth, it is necessary that a piece of animal tissue be added to the medium. Fermentation of glucose, lævulose, maltose and glycerine occurs, with acid formation.

Composition of cystine agar.—Cystine agar consists of beef-infusion agar, having a *p*H of 7·6, to which 0·02 per cent. of cystine is added, after which it is sterilized for fifteen minutes in a steam sterilizer, and subsequently incubated for twenty-four hours to ensure sterility.

Cultures of *B. tularense* are extraordinarily infectious, and should be handled with great care.

In its serum reactions cross-agglutination occurs in connection with *Brucella melitensis* and *Br. abortus*. About 23 per cent. of tularæmia sera do so, and about 35 per cent. of undulant fever sera agglutination *B. tularense* to some degree. Concentrations of the organism are best obtained from emulsions made from the spleens of infected mice or guinea-pigs.

The organism is pathogenic for guinea-pigs, rabbits, white rats, mice, ground-squirrels (*Citellus beecheyi*), gophers (*Thomomys bottæ*), and *Macaca* monkeys ; while brown rats (*R. norvegicus*), horses, calves, pigs, goats, cats, dogs, fowls and pigeons are found to be refractory. The organism can be transmitted by *Chrysops discalis*, as well as by the stable-fly *Stomoxys calcitrans*, the bed-bug, *Cimex lectularius*, the squirrel-flea, *Ceratophyllus acutus*, the rabbit-louse, *Hæmodipsus ventricosus*, and the mouse-louse, *Polyplax serratus*.

Ticks can also act as vectors—*i.e. Dermacentor andersoni*, *D. variabilis*, *D. occidentalis*, *Ixodes ricinus*, var. *californicus*, Banks, and the rabbit tick (*Hæmaphysalis leporis-palustris*). Four species of mosquito, *Aëdes* and *Theobaldia*, have been shown to transmit *B. tularense* under experimental conditions. In Sweden *Aëdes cinereus* does so in nature.

Dermacentor andersoni is particularly important, *B. tularense* being found in the intestinal lumen, in the cells of the gut wall, in the body fluids, and in the fæces. The organism is harboured throughout the winter months and infection is transmitted to the eggs of the tick.

The disease occurs as a natural infection in wild rodents. In America the most important reservoirs of infection are the cotton-tail rabbit (*Sylvilagus*), the jack-rabbit (*Lepus*), and the snowshoe-rabbit (*L. bairdi*); other reservoirs are the Californian ground-squirrel, wild rats, and meadow mice (*Microtus californicus*). The beaver is also suspected. It is probable that the opossum and coyote may play a part; also the ruffled grouse (*Bonasa umbellus*) and the sage hen (*Centrocercus urophasianus*) (Montana), which are infected with the bird-tick, *Hyalomma cinnabarina*. In fact, this disease has been held responsible for the disappearance of these beautiful birds in parts of America. In Europe and Siberia the hare, rabbit, lemming, musk and water rats, the suslik, and field vole are reservoirs.

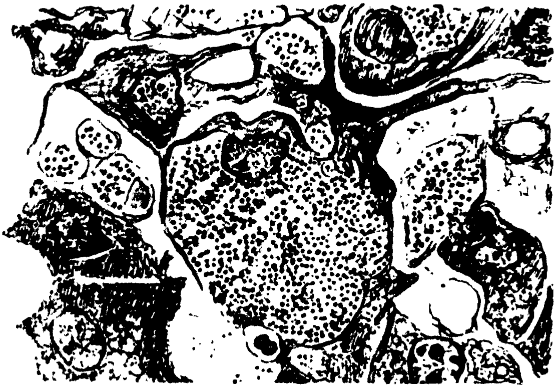


Fig. 52. Tularæmia. Section of liver showing aggregation of *P. tularensis* in hepatic cells.
(*After Prof. R. P. Strong*)

Man is extremely likely to contract the disease from animals, consequently laboratory infections are very frequent.

The nasal secretion and the urine of infected mice and rabbits are infective for other animals.

Pathology.—In animals there is usually a fatal septicæmia. The pathological appearances of infected guinea-pigs and rabbits at autopsy much resemble those of plague in the same animals. In an experimentally-infected guinea-pig there is hæmorrhagic œdema at the site of inoculation, with blood-stained peritoneal exudate, and diffusely enlarged spleen, in which characteristic small necrotic foci can be found. Similar lesions may be detected in the liver; on microscopic section of these organs a dense infiltration with polymorphonuclear cells can be found, but the organisms can with difficulty be detected (Fig. 52). In the spleen of the mouse, on the other hand, little or no leucocytic response occurs; and when stained with Twort's light-green neutral-red stain, *B. tularense* can be readily demonstrated in large numbers. (Fig. 52.) In the few recorded fatal cases in man nodules have been found in the lung and spleen.

Symptoms.—The incubation period appears to be from one to ten days. Unrecognized cases of tularæmia are probably common in the endemic areas, for it may occur as a generalized disease without local lesions, or local lesions may be present with secondary lymphadenitis, which may not cause grave constitutional disturbances. As a rule, in the cases which have been so far recorded, a definite fever is present. The onset is sudden, with headache, backache, and fleeting pains, remarkable lassitude, and pyrexia which may last for three weeks or more; the extreme range of temperature is about 104° F. The pyrexia may subside to normal, or nearly so, from the third to the sixth day. The pains commence at some particular point, and persist for two weeks to a month, though localized ones of greater or lesser degree may recur for the succeeding twelve months. Epistaxis and dizziness are common; weakness and lassitude persist for weeks after the pyrexia has subsided, and it may be months before normal health is restored. The spleen is not palpable. Typhoidal tularæmia has been observed in about 5 per cent. of cases.

Such is the description of the generalized disease as it is met in man. When infection results from inoculation, the effect may be purely local; an inflamed papule occurs at the site, with secondary lymphadenitis. After the bite of an infected chrysops, or other fly, on some exposed surface of the body, the onset is sudden, with pains and fever. The initial ulcer, which may develop within 48 hours, presents a process of diffuse necrosis with infiltration of the base. Sometimes subcutaneous nodules resembling sporotrichosis appear on the anterior and posterior aspects of the forearm and along the lymphatics between the ulcer and the regional glands. They are firm, movable and tender, and 4–10 mm. in diameter. The patient may be prostrated and have to retire to bed; the lymph-glands draining the bitten area subsequently become inflamed and swollen, and suppuration may occur. Subcuticular roseolar rashes on the body and arms are sometimes observed in Western America. Nodular and pustular lesions have also been recorded.

Three cases of laboratory infection of tularæmia have been recorded in England. Though the debilitating effect is very marked, only one death, in a series of seven cases reported from Utah, has been recorded, and this took place from apical pneumonia. There is, apparently, a lasting immunity in man. There is no record of a second generalized attack, though, as in Francis himself, a local re-infection may occur.

Infections of the eye and conjunctiva, causing acute conjunctivitis, were recorded by Vail, Lamb, and others. In America, an ocular-glandular process is well recognized. The primary lesion is of the conjunctiva and there is a regional lymphadenitis of the head and neck. Severe conjunctivitis results, with chemosis and œdema of the lids and surrounding tissues. There is now little doubt, as pointed out by Herrenschwand (1935), that "Parinaud's conjunctivitis," first described in Paris in 1889, is none other than ocular-glandular tularæmia. Parinaud recognized that it was infectious and that it was associated in some manner with animals. It is characterized by the granular condition of the lids, with chemosis of the conjunctiva, inflammation and enlargement of the pre-auricular lymphatic glands. In 1917 and 1918 Herrenschwand observed two cases in Austrian soldiers, and isolated a bacillus pathogenic to guinea-pigs (undoubtedly *B. tularense*); a small portion of a culture, accidentally dropped into the canthus of the eye, immediately produced typical conjunctivitis.

Diagnosis.—This disease is most readily reproduced by inoculating material from the patient's ulcer, or gland-juice obtained by aspiration, into guinea-pigs, mice, or rabbits, thereby producing generalized tularæmia in these animals, from whose tissues the organism may be isolated on special media. The organisms are rarely present in the blood of human cases. Agglutination tests can readily be performed: the serum of patients suffering from the disease will agglutinate suspensions of the organism in high dilutions but, as pointed out by Ledingham, where cultures of *B. tularense* cannot be obtained, the spleens of infected mice contain the organisms in such large numbers that an emulsion in formalinized citrate solution may be used instead. Agglutination occurs in the second week, reaching its maximum between the fourth and eighth weeks, when there is a gradual fall, but it may persist for eleven years.

It has been ascertained that a cross-immunity frequently co-exists between tularæmia and the undulant fevers. Calder stated, too, that tularæmia serum agglutinates *Proteus OX*19 in a dilution of 1 : 80 and over in 13·5 per cent. of cases.

An intradermal test with a suspension of killed organisms has also been introduced.

The differential diagnosis of this condition has to be made from plague and from rat-bite fever. In both cases alike it depends upon the recognition of the respective specific organisms.

Treatment.—This is mainly symptomatic. The patient should be kept in bed for several weeks after the subsidence of the fever. Convalescence should be prolonged. The inflamed glands should be dressed with a saturated aqueous solution of magnesium sulphate. Incision is inadvisable, unless suppuration is observed.

Foshay (1940) reported on the effects of serum treatment of 600 cases within six years. Sera were prepared from goats by injection with two highly virulent strains of *B. tularense* and 10–15 c.c. injected intravenously or intramuscularly into children, 30 c.c. into adults.

Prophylaxis.—Prevention depends in part upon the avoidance of contact with infected rabbits in the endemic area. The dangers of experimental work with *B. tularense* in the laboratory have already been sufficiently emphasized. The prevention of the disease, from the public health point of view, is by no means easy. Sick or dead rabbits must be handled with great caution, and rubber gloves must be worn by laboratory workers, marketmen, cooks, etc., in view of their great liability to infection. Cooking destroys the infection, as does also prolonged freezing.

CHAPTER XIII

MELIOIDOSIS

Synonyms. Stanton's Disease ; Pneumo-enteritis ; Pseudocholera.

Definition.—This is a rare, glanders-like disease occurring in Burma, the Malay States and possibly Ceylon. The name melioidosis was suggested by Stanton and Fletcher in order to describe its close relationship to glanders (μηλίς, used by Aristotle for a "distemper of asses" and εἶδος = form.) Melioidosis has many resemblances to tularæmia ; both are diseases of rodents accidentally attacking man.

History and geographical distribution.—This disease is due to *Bacterium (Pfeifferella) whitmori* (Whitmore, 1911), found at autopsies of beggars in Rangoon. In 1917 Stanton and Hennessy found similar organisms in patients dying from choleraic symptoms. According to Krishnaswamy the disease is specially common in Rangoon. Other cases have been found in Singapore and in Saigon and, according to Duke, it may occur in Uganda. In 1913 the infection appeared as an epizoötic amongst the laboratory animals at Kuala Lumpur.

Ætiology.—*Bacterium whitmori* (sometimes known as *Actinobacillus pseudomallei*) closely resembles *B. mallei* ; it is a small bacillus about the same size and shape, and occurs in very large numbers in all acute lesions of the disease. In films stained by Leishman's method, bipolar staining is very common. Acid-fast granules, decolourized by alcohol, were described by Mayer and Finlayson (1944). On culture also it resembles the glanders bacillus very closely, but is more actively motile and liquefies gelatin more rapidly. It grows luxuriantly upon peptone agar, forming a dense wrinkled culture, especially when the medium contains glycerin ; on broth cultures a pellicle is formed. Brown, Duncan and Henry have shown that *B. whitmori* can be distinguished from *B. mallei* by its behaviour on a peptonized medium containing 1 per cent. sodium fumarate. This organism is pathogenic for most laboratory animals ; for guinea-pigs, at any rate, the infection is more rapidly fatal than glanders, but in each case, in the male, acute orchitis is produced on intraperitoneal injection—the so-called Strauss reaction.

Susceptible animals can be infected by scarification, by feeding or by simple application of cultures to the nasal mucosa ; a characteristic feature in infected animals is discharge from the nose and eyes.

The organism is excreted in the urine and fæces of infected laboratory animals, while several cases of natural infection, especially in rats (*Mus griseiventer*, Bonhote), cats and dogs, have been observed. In 1927 the first case was reported in a horse from the Malay States, when the bacillus was isolated from nasal pus.

Pathology.—The lesions vary very considerably. Numerous small pulmonary abscesses, roughly resembling those of miliary tuberculosis, are produced. Nodules which coalesce and break down into abscesses are found in the liver ; they somewhat resemble those of portal pyæmia, and have to be distinguished from amœbic abscesses. The organisms have been recovered from the blood, urine, sputum, and fluid from cutaneous vesicles of patients dying from the disease. In laboratory animals, artificially infected, small nodules form in the internal organs.

Symptoms.—The accounts so far published of the symptomatology are meagre. The first cases observed by Stanton in 1917 were suffering from an acute diarrhœa, with collapse roughly resembling that of cholera, and it appears that several patients who recovered from the initial intestinal attack died later from a form of septicæmia with pulmonary lesions resembling tuberculosis. During 1921 a few more cases were encountered, with similar symptoms. Only two are known to have recovered. There is usually a high remittent and somewhat irregular pyrexia. Delirium and mania appear to be frequent terminal symptoms. What appears to be a chronic form of the disease is also recognized : in this the lesions are found in the skin and subcutaneous tissues, leading to cutaneous abscesses and collections of pus in the liver, lungs, and spleen. The initial signs may be those of acute parotitis. A peculiar case has been reported in England (1948) by Grant and Barwell in a soldier who had served in Malaya. A latent period of three years elapsed between possible infection with *B. whitmori* and the onset of clinical manifestations. The case was characterized by parotid swellings, abscesses, osteomyelitis of frontal bone, perispinal abscesses and bronchopneumonia. A second and almost identical case was diagnosed in a British soldier in South Africa in 1944. He had served in Singapore (Mayer and Finlayson). Very few cases have been recognized in women, but in them the brunt of the disease falls upon the bladder and kidneys. The disease is said to be specially common in morphia addicts, but this is probably a coincidence. How man is infected, as a general rule, is still uncertain.

Diagnosis.—This is obviously best carried out by isolation of the bacillus from the fæces, urine, or blood, and differentiating it from the glanders bacillus. In one instance the organism was obtained from the cerebro-spinal fluid (P. H. Martin). Stanton and Fletcher found that the blood-serum agglutinated cultures of the organism in high dilution (1 in 2500 to 1 in 8000), a fact which is extremely useful in diagnosis. Differential diagnosis from malaria, typhoid, dysentery, tuberculosis, plague, cholera and even liver-abscess, may have to be established. There are several resemblances to tularæmia, and both are characterized by pyæmic nodules.

Differential diagnosis from glanders is more complicated. Patients infected with *B. whitmori* give a positive reaction to *mallein*, whilst horses infected with melioidosis give a negative test. Central chemotaxis and slight tendency to extension of the lesions, characters regarded by McFaydean as peculiar to glanders, are found in melioidosis.

Prognosis.—Most patients die within ten days of the onset : in chronic cases they may be ill for three to eight months or longer.

Treatment.—Cases were treated by Stanton with autogenous vaccines, which are said to modify the acuteness of the disease. In the English case reported above, sulphadiazine in large doses reduced the activity of the organism, but failed to eradicate the localized foci of infection.

CHAPTER XIV

THE UNDULANT FEVERS (BRUCELLOSIS)

Preliminary statement.—Originally the term undulant fever was employed to designate a type of fever, commonly found in Malta and the Mediterranean area generally, which was usually referred to in medical literature as "Malta fever." Experience, however, has shown that several closely allied fevers are to be classified under this heading. These fevers are due to infection by organisms of the genus *Brucella*. The following varieties of these organisms and their associated fevers are now recognized:

1. *Brucella melitensis* (formerly known as *Micrococcus melitensis*) which is originally a parasite of the goat and which is usually conveyed to man in goat's milk.
2. *Brucella abortus* (formerly known as *Bacillus abortus*, Bang) which is an affection of the cow, in which it causes abortion. A strain (*Brucella suis*) also occurs in the pig.[1] The infection appears to be conveyed to man through cow's milk.

Although *Brucella melitensis* infections have more or less a tropical and subtropical distribution, those of the abortus type are found all over the world, wherever epidemic abortion amongst cattle occurs.

I. UNDULANT FEVER (MELITENSIS TYPE)

Synonyms. Febris Undulans; Malta Fever; Mediterranean Fever; Gastric Remittent Fever.

Definition. A disease of low mortality, indefinite duration, and irregular course, undulant fever is the result of infection by a specific germ—*Brucella melitensis*. In its more typical form it is characterized by a series of febrile attacks, each individual one, after lasting one or more weeks, gradually subsiding into a period of absolute or relative apyrexia, also of uncertain duration. Common and characteristic complications are a rheumatic-like affection of joints, profuse diaphoresis, anæmia, liability to orchitis and neuralgia. Although only occasionally fatal, the disease is a fruitful source of inefficiency and invaliding.

History and geographical distribution.—Formerly confounded with typhoid and malaria, undulant fever has been established as a separate disease by the labours of various observers—Bruce (1887), Hughes, Gipps, Wright, Semple, and Bassett-Smith. Undulant fever appears to be more widely distributed than was formerly thought. It is not confined to Malta, or even to the Mediterranean; it may occur in Italy, France, Spain, the Red Sea littoral, India (Punjab), China, South Africa, Somaliland, West Africa, the West Indies, the Philippines, South America, and the United States, especially in New Mexico and Texas. Duke (1940) reported the isolation of *Br. melitensis* from cow's milk in Staffordshire, England. Owing to the close relationship between *Br. melitensis* and *Br. abortus*, and the clinical resemblance between the two forms of fever they produce in man, it is extremely difficult to state the exact geographical range of each.

---

[1] Another species of Brucella is found in pigs (*Br. bronchisepticus*)—but there is no reason to believe that it is communicable to man.

Epidemiology and endemiology.—The following figures, supplied by Bassett-Smith, show the importance of undulant fever in former years to the British naval and military services in the Mediterranean:

INCIDENCE OF UNDULANT FEVER

	Army			*Navy*			Total days sickness
	Strength	Cases	Deaths	Strength	Cases	Deaths	
1900	9,203	171	10	14,250	356	6	22,998
1901	9,384	288	10	14,070	286	3	16,987
1902	10,889	198	10	18,470	436	3	27,432
1903	10,608	507	11	18,410	400	6	30,541
1904	10,615	429	15	19,590	430	9	28,458

The most susceptible age is between the sixth and the thirtieth year. Length of residence does not influence susceptibility. In Malta the natives suffer as well as visitors, while there, and in other places where the disease is endemic, it occasionally assumes an epidemic character. The period of its greatest prevalence is the season of lowest rainfall, embracing June, July, August and September, the disease differing in this respect from typhoid which, in Malta, is more prevalent during the succeeding months, but a few cases may occur all the year round. This is explained, not only by the greater use of goats' milk during the summer months, but also by the fact that, following the birth of the kid in spring, contamination of the milk is more marked. The goats are not necessarily ill, except for their liability to abort. The disease tends to occur in particular towns or villages, in particular houses, barracks, hospitals, and rooms, and in particular ships, manifestly originating in limited foci of infection. Certain ships were formerly notorious foci of the disease. All classes were liable: the officer and his family as well as the soldier in barracks or the sailor on shipboard. The organism has been found in mothers' milk, so may presumably be transmitted to sucklings.

It is not correct to assume, as has so often been done, that because of these essential discoveries, undulant fever has been banished entirely from Malta. The cases amongst the British military and naval population dropped from 245 in 1905 to 12 in 1907, but during the years 1929–35, there was a great increase in the number of cases among the civil population. Gatt (1938) reported that among the latter the incidence of the disease increased till 1934, when as many as 7·25 per mille were infected. Among the indigenous inhabitants there is a deep-rooted prejudice against boiling milk, and they are not content unless the goats are actually milked on their doorstep. However, tinned preserved milk is coming rapidly into favour among the poorer inhabitants as an infant food.

Undulant fever is not, generally speaking, transmitted directly from one person to another; that is to say, is not, as a rule, directly communicable from the sick to the healthy. The germ is readily conveyed by inoculation; the prick of a contaminated needle will suffice. Moreover, it is a well-recognized fact that undulant fever is the most easily acquired in the laboratory from handling cultures. An outbreak of 45 cases in a bacteriology class, of which one ended fatally, was reported by Huddleson and Munger (1940) in Ohio. In this case the actual method of infection could not be determined. Living emulsions of the micro-organism should never be handed round for class work; similarly, infection may be conveyed by sucking a thermometer recently used by a patient. A very striking circumstance is that in some hospitals the nurses and attendants in the fever wards are ten times more liable to the disease than people not so employed.

Milk.—It is now known that the infection is most usually conveyed in milk, and it has been suggested that it may be introduced in other kinds of food, or in water. Facts pointed very distinctly to goat's milk as the most important medium. The organism was present in the milk of 10–50 per cent. of Maltese goats, and monkeys were easily infected by feeding them on it. Directly the goat's milk supply to the naval and military hospitals in Malta was stopped, the cases of locally-acquired undulant fever practically ceased. Formerly this fever was very common in Gibraltar. The milk supply of the garrison at that time was largely from animals imported from Malta. Gradually these goats have died out or been got rid of, and no more have been imported. Concurrently with this there has been a marked and proportional reduction of undulant fever cases in the garrison, so that, as a cause of disability, it has now quite disappeared from the records of the British Army and Navy. There is one well-authenticated instance of wholesale infection from this source in the s.s. *Joshua Nicholson*, which shipped 65 goats in Malta; an epidemic of undulant fever broke out on board, and nearly all those who drank the milk of the goats were attacked.

Cheese.—There is a considerable amount of evidence that undulant fever can be acquired by eating cheese made from the milk of infected goats. Several varieties of cream cheese made in the South of France, and even ripened cheese such as Camembert, have fallen under suspicion.

Manure.—In the department of Aude near the Pyrenees, infection by handling manure soiled by urine of infected goats and sheep is regarded as possible.

Ætiology.—Bruce in 1887 demonstrated the presence in the spleen in undulant fever of a special bacterium—now called *Brucella melitensis*—and, by a series of experiments, proved that it was the cause of the disease. Unfortunately, as the bacterium occurs only sparsely in the general circulation (unless in the earlier stages, when the temperature is high), to search for it in the blood in the later stages does not aid diagnosis. The organism is present in abundance in the spleen pulp, and also in the lymphatic glands, in which it persists longer than elsewhere, and from both of which it can be recovered by cultivation. Bruce found it in the spleen in ten fatal cases. His results have been confirmed by many other observers. Injections of pure cultures give rise to a similar disease in monkeys and other animals, from whose blood the bacterium can be recovered, cultivated afresh, and injected into other animals, when it will again give rise to the disease. In five recorded instances, inoculation—intentional and accidental—of cultures of the bacterium into man has been followed by the characteristic symptoms after an incubation period of from five to fifteen days.

A variety of this organism, *Brucella paramelitensis*, which gives different serological reactions from those of the original strain, has been recognized as responsible for those cases of clinical undulant fever in Tunis and Algeria which do not give a high agglutination reaction with cultures of *Br. melitensis*.

Br. melitensis measures 0·33 μ in diameter. It occurs generally singly, often in pairs, sometimes in fours, but never, unless in culture, in longer chains. It is Gram-negative and readily stained by a watery solution of gentian-violet, and is best cultivated in a 1½ per cent. very feebly alkaline peptonized beef agar; in this medium, some time after inoculation, it appears as minute, clear, pearly specks. After thirty-six hours the cultures become a transparent amber; later they are opaque. No liquefaction occurs in gelatin. The individual colonies are small, round, somewhat raised discs growing to 2–3 mm. in diameter about the ninth day. The optimum temperature for growth is 37° C. In bouillon it may produce a general turbidity. As a rule, the organism cannot be cultivated under anaërobic conditions. Recently, it has been discovered that the vitamin complex known as *biotin* is essential for its growth. No indol is formed, and the organism does not ferment glucose. Milk and other media are rendered alkaline.

At one time, *Br. melitensis* was believed to be a delicate organism, but investigations have shown that it can live for a long time in water, in dust, or on the clothes of patients, and that it is not killed by cold or desiccation. Moreover, it is now known to be excreted in the urine of man in 10 per cent. of convalescent cases, and to occur in great abundance in the milk and urine of apparently healthy Maltese goats (50 per cent.), and probably of some cows. It has also been found in dogs (9 per cent.), sheep and horses. These facts account in part for the great frequency and dissemination of the disease in such insanitary places as Malta, to which place they specially refer.

Br. melitensis can be cultured from the blood-stream during the height of the fever in a considerable proportion of cases. A liver infusion—Staffseth's medium—is now commonly employed as selective culture medium. It has occasionally been obtained from the fæces. The serum of undulant fever cases of this and the *Br. abortus* type, as well as the milk of infected goats, will agglutinate it. The organism has been recovered from the gall-bladder by Eyre. Amongst the smaller laboratory animals, the guinea-pig is highly susceptible to inoculation, a minute intraperitoneal dose causing prolonged infection.

Br. melitensis was stated by Evans, Myer, Shaw, and others to be morphologically, culturally, and serologically similar to *Br. abortus*. Three strains, *melitensis*, *paramelitensis*, and *abortus*, are separable one from another only by tests of agglutinin absorption. This criterion must be applied to infections in animals and in man in order to determine their ætiology. Cultures of *Br. abortus* are agglutinated in high dilutions of the serum of patients suffering from *melitensis* undulant fever.

It is well known that *Br. melitensis* may produce abortion in goats, though the animals themselves may exhibit no other clinical changes.

In monkeys intramuscular injection produces within three days a rise of temperature and death within three weeks. According to Burnet and Conseil, *melitensis* is at least a thousand times more pathogenic for these animals than is *abortus*. Indeed, only enormous doses of *abortus* will produce any effect at all in small monkeys.

Pathology.—The disease has almost no pathological anatomy. The spleen is the only viscus which is distinctly diseased. This is enlarged (average 17 oz.), soft and diffluent; on microscopical examination the lymphoid cells are found to be increased. There may be some congestion and even ulceration of the intestinal mucosa, but this is not an essential feature. Other organs show chiefly cloudy swelling, and glomerular nephritis may be present.

Symptoms.—The period of *incubation* in the naturally-acquired disease is difficult to fix. Cases have occurred as early as six days after arrival, others as late as fourteen and seventeen days after leaving Malta. Some hold that the disease may remain latent for months. It begins generally with lassitude and malaise, such as is associated with the incubation of many specific fevers, particularly typhoid. There are headache, bone-ache, anorexia, and so forth. Pain in the eyes, especially on lateral movement, is very characteristic. There may also be a peculiar sensitiveness of the alveolar margins of the jaw and painful movement of the temporo-mandibular joint. At first the patient may go about his work as usual. Gradually the daily task becomes increasingly irksome, and he takes to bed. Headache may now become intense, and, in addition, the patient suffers from thirst and constipation. At the outset the symptoms, except that there is very rarely diarrhœa, resemble those of typhoid, and epistaxis is not uncommon. There are no rose spots, however, then or at any subsequent period. There is evidence, in the coated tongue, which looks as if covered with white paint, in the congested pharynx, the anorexia, and the epigastric tenderness, of gastric catarrh; and the occasional cough and harsh, unsatisfactory breathing at the bases of the lungs indicate some degree of bronchitis or of pulmonary congestion. There may also be delirium at night, but as a rule there is insomnia. The fever is usually remittent, the temperature rising about midday (generally about 2 p.m.) and falling during the night, and the patient becoming bathed in a profuse perspiration towards morning. The spleen and the liver, but especially the former, are somewhat enlarged and, perhaps, tender. Lumbar pain may be severe.

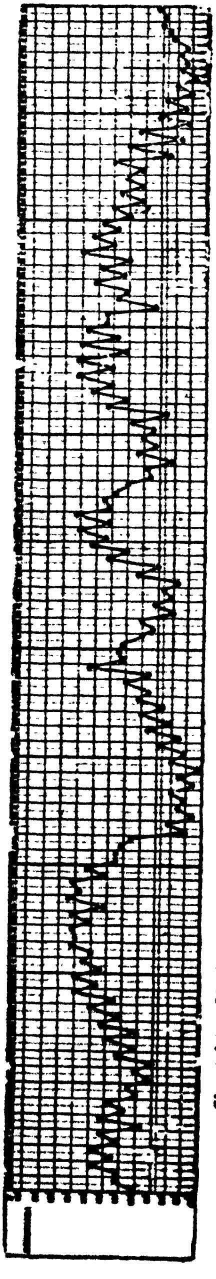


Chart 14.—Undulant fever: typical case. (*By permission of London School of Hyg. and Trop. Med.*)

After a week or two of this type of fever, specially distinguished by pains and perspirations, the tongue begins to clean and the appetite to revive; but, notwithstanding these signs of amendment, the patient still remains listless and liable to headache and constipation. He continues feverish and at times perspires profusely. Gradually, however, although he is anæmic and weak, subjective symptoms become less urgent; he then sleeps well, he has no delirium at night, and can take food, although the body-temperature may still range slightly above the normal. Then once more, and perhaps over and over again, fever with all the former symptoms gradually returns; and now, if it has not declared itself before, the peculiar fleeting rheumatic-like affection of the joints or fasciæ, so characteristic of the disease, shows itself in a large proportion of cases. One day a knee is hot, swollen, and tender; next day this joint may be well, but another is affected; and so this metastatic, rheumatic-like condition may go on until nearly all the joints of the body have been involved one after the other. Effusions have been reported from which *Brucella* has been cultured. Purulent synovitis of the costosternal and costochondral joints sometimes occurs. Arthritis and osteitis of the foot with bone atrophy and blurred contours of the joints between the cuneiform and metatarsal bones were described by Weil. The patient may suffer also from neuralgia in different nerves—intercostal, sciatic, and so on. Orchitis is an occasional early complication, and may be mistaken for testicular mumps. In some cases these complications are severe and characteristic; in others they may be mild, or absent altogether. In this respect the same infinite variety exists as in other specific fevers. In severe cases a purpuric condition with bleeding from the gums is occasionally observed.

The most characteristic feature of undulant fever is the peculiar behaviour of the temperature (Chart 14). In a mild case there may be a gradual ladder-like rise through a week or ten days to 103° or 104° F., and then through another week or so a gradual ladder-like fall to normal, the fever, which is of a continued or slightly remitting type, disappearing for good without complication of any sort in about three weeks. Such mild cases are the exception. Usually, after a few days of apyrexia, absolute or relative, the fever wakes up again and runs a similar course, the relapse being in its turn followed by an interval of apyrexia, which is again followed by another relapse; and so on during several months. This is the "undulant" type from which Hughes derived the name he suggested for the disease—*febris undulans*. A factor of practical importance from the diagnostic point of view is the tendency for the fastigium of the temperature curve to occur towards midday or early afternoon; this feature distinguishes it from typhoid, in which the maximum rise generally occurs towards 6 p.m., or from other long-continued septic fevers, such as that in hepatic abscess, in which this takes place towards night-time.

In cases of another class a continued fever persists for one, two, or more months, with or without the usual rheumatic, sudoral, and other concomitants—the "continued" type of Hughes.

Usually remittent or nearly continued in type, in a proportion of instances (generally *paramelitensis* infections) the fever exhibits distinct daily intermissions, the swinging temperature chart suggesting sepsis, endocarditis, or malaria. This is the "intermittent" type of Hughes.

In some patients, two to three months may elapse before they are finally rid of the tendency to febrile attacks and characteristic pains and aches. According to Bassett-Smith, the average duration of the disease is four months, but it may last two years. The shortest period is about three weeks.

As in other bacterial diseases, cases of all degrees of severity are met. Bassett-Smith recognized five types:

(*a*) *Ambulant.*—The patients have no symptoms, but are excreting *Br. melitensis* in their urine and are naturally potential sources of infection.

(*b*) *Mild cases.*—These last about a fortnight and are apt to be mistaken for paratyphoid.

(*c*) The *ordinary type.*

(*d*) The *malignant type*, with hyperpyrexia and toxæmia. This may be fatal, and considerable difficulty may be experienced in making a diagnosis, as in the case reported by Archibald in which death took place on the twenty-seventh day.

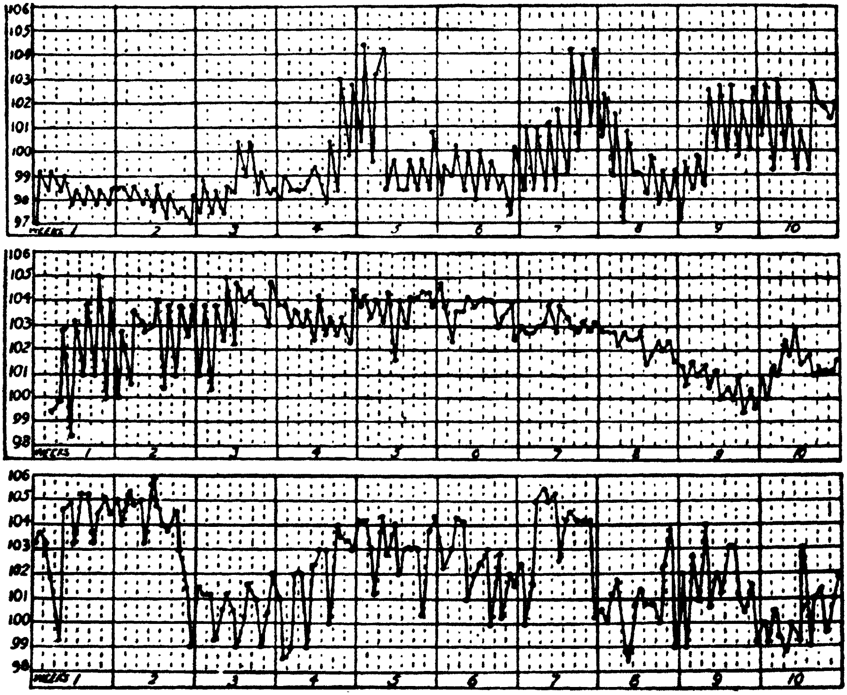


Chart 15.—Various types of temperature chart in undulant fever.
(1) intermittent type
(2) remittent type
(3) irregular type

(*e*) An *intermittent type* with hectic fever, sweats, and general wasting. This is apt to be mistaken for tuberculosis, and appears to be common in South Africa.

As a rule, there is a moderate leucopenia (about 6,000 per c. mm.) with an increase of lymphocytes. Sometimes also a slight secondary anæmia is observed.

Surgical Brucellosis.—Hydrarthrosis of a single joint cavity and superficial abscess formation on the chest or abdomen, without generalized fever, may also be produced by *Br. melitensis*. The Editor has seen one such case from Somaliland where, had not the organism been isolated from the abscess pus, this possibility could never have been suspected. Chronic infection resulting in osteomyelitis of the long bones has been recorded.

Complications and sequelæ.—As a rule, by far the most serious consequences of undulant fever are the debility, the emaciation, the profound anæmia, the rheumatic-like pains, the neuralgias, and such sequelæ as abscess, orchitis, mastitis, parotitis and boils. In the male, intermittent hæmorrhages from the urethra are not uncommon. Orchitis is estimated to occur in four per cent. of cases. In women the disease is apt to give rise to ovarian pains, dysmenorrhœa, amenorrhœa and menorrhagia, and to favour abortion and premature labour. The germ may pass into the fœtus ; children born in such circumstances are weakly.

Complications, such as splenic and hepatic enlargement, enlargement of the mesenteric and cervical glands, suppuration, phlebitis, chorea, various psychoses, arteritis, endocarditis, pericardial effusion, melæna and hæmaturia, are met occasionally during the long course of the disease. When death occurs it is usually from suddenly developed hyperpyrexia ; occasionally it is brought about by exhaustion, by hæmorrhages and purpuric conditions, or by some pulmonary complication such as pneumonia. Fatal gastric and intestinal hæmorrhages have been described on many occasions. In a few instances the fever is a fulminating type, rapidly ending in death from hyperpyrexia.

A comparatively common sequel is chronic inflammation of the sacro-iliac joint.

Diagnosis.—The diagnosis of undulant fever from typhoid is an important practical matter and may be difficult in the early stages. Reliance has to be placed principally on the characteristic temperature curve, the presence or absence of rose spots, of diarrhœa, of joint complications, and of sweats, the locality where and the season in which the disease was contracted, and the agglutination test. There may be considerable hesitancy in differentiating it from pulmonary tuberculosis, especially in the intermittent form, and there are cases of undulant fever with pulmonary signs and symptoms which may resemble that disease. Undulant fever, moreover, may " light up " a quiescent tuberculosis.

An *intradermal* or " melitene " reaction (Burnet, 1922) has been introduced. For the purpose, 0·2 c.c. of a killed broth-culture, containing half a million organisms, is injected into the skin. If the reaction is positive, a red œdematous area results at the site and persists for several days. Adequate controls with broth and cultures of other organisms should be performed in adjacent areas of skin. According to Nattan-Larrier the melitene reaction is best performed by injecting $\frac{1}{10}$-$\frac{1}{20}$ c.c. of the filtrate of a 20 days' broth culture into the skin 4 in. above the elbow. In typical cases the reaction, which consists of a red plaque 4–6 cm. in diameter, becomes positive in six hours and persists for two days. The reaction is positive on the seventh to tenth day of the fever and persists for ten months after recovery. It has been asserted by Wilson and others that, if this reaction is repeated, abscess formation may result ; even gangrene of the skin has been observed.

Hæmoculture.—As early as the second day of the disease the organism may be recovered from the blood-stream. For this purpose 5–10 c.c. of blood should be drawn off by means of an aseptic syringe and with great precaution distributed into several flasks of broth. The broth should be incubated at least twenty-four hours, or, if necessary, for as long as 26 days, and subcultures made from time to time on trypsin-agar slopes. On the fifth day, on further incubation, minute dewdrop-like colonies should become apparent, and the emulsion should be tested against a specially prepared immune serum in dilutions from 1 in 40 to 1 in 400. It is said that cultures from the blood-clot may sometimes give better results than those from the whole blood. The organism may be obtained by splenic puncture, though this method is rarely justifiable.

Isolation from the urine.—This is much more difficult to obtain than from the blood. The urine must be obtained either by catheter or midstream specimen after the fifteenth day of the disease. Every precaution must be taken to prevent contamination, to which *Br. melitensis* is very sensitive.

Agglutination test.—Agglutination, if performed by the macroscopic method and with modern technique, will generally give positive results. There are several important points to remember in connection with this reaction.

Strain of organism employed for agglutination.—The serum, as a rule, contains no agglutinins until after the second week of the disease. It may be necessary to employ several strains of *Br. melitensis*, as well as cultures of *Br. paramelitensis*. Titres of agglutination as high as 1 in 6000 have been reported.

As other sera are known to agglutinate the organism in low dilutions, it is recommended that the blood be heated to 56° C. for half an hour before being used for the test, in order to destroy non-specific agglutinins. The occurrence of a pro-agglutinoid zone (or zone of no reaction) may be a source of error, but only in higher dilutions, and it is possibly due to the presence of anti-agglutinins. It is necessary, therefore, to employ a considerable number of dilutions (*see* p. 1014).

According to Ledingham, the serum of tularæmia agglutinates *Br. melitensis*. A problem of differential diagnosis may arise when a serum agglutinates both *B. tularense* and *Br. melitensis* in equal titre. This can only be settled from a serological aspect by testing for the absorption of agglutinins.

Complement fixation test.—No distinct advantage has been reported for this method over the agglutination test. It is, moreover, more complicated. Often the serum is found to be anti-complementary. The technique is identical with that employed for the standard Wassermann test except that *melitensis* or *abortus* antigens are used.

After the fever has gone on for several weeks, diagnosis is, of course, easier; in the early stages, on clinical grounds alone and, apart from the agglutination test, it may be, as already stated, almost impossible. Tuberculosis, abscess, empyema, malaria, relapsing fever, acute rheumatism, and all the causes of continued high temperature of a septic type have to be carefully excluded in attempting a diagnosis. The possibility of the concurrence of another infection—typhoid, for example—must not be overlooked.

Prognosis.—As a general rule, in military and naval forces the mortality-rate is low, from 2 to 6 per cent., but in the civilian population it may be considerably higher. Death may occur from hyperpyrexia, heart-failure, or pulmonary complications. Bassett-Smith pointed out that a persistent temperature of 104° F. may indicate a grave prognosis, as may also an intermittent pulse. Alarming symptoms may develop at any stage of the disease, especially in relapses. Though it may be unwise to forecast how long a fever may last, yet, when the pyrexia has subsided for more than ten days, and the patient's tongue is clean and his appetite good, no further relapses may be expected; but there is frequently a short terminal rise of temperature.

In the malignant type the death-rate may be 10 per cent. or more. A persistent temperature of 104° F. and an intermittent pulse are grave, as are also pneumonic complications. The after-effects of the disease are often incapacitating, especially the production of neurasthenia, neuralgia and cardiac weakness. The debility makes the convalescent an easy prey for any intercurrent disease. It is normally considered that, as a general rule, a lasting immunity is conferred by one attack.

Treatment.—When the diagnosis is sure it is well to give a purge—none better than calomel and jalap—and to instruct the attendants to keep the patient's temperature systematically below 103° F. by cold sponging with vinegar and water or, if necessary, by cold bath or by ice variously applied. In view of the prolonged nature of the fever this measure is important; at the same time, such treatment need not be applied too energetically, or so as to depress: a fall of 2° or 3° is all that is desirable.

Phenacetin and similar antipyretics are also often given to bring down temperature; but the wisdom of employing depressing drugs in so chronic and asthenic a disease is, to say the least, questionable. Threat of hyperpyrexia is best met by early sponging, the wet pack, or, if necessary, the cold bath. Sleeplessness may demand hypnotics, such as trional, veganin, or allonal; headache, if severe, is relieved by moderate doses of phenacetin, pyramidon, or a similar drug; inflamed joints or testes by the usual local applications; constipation by enemata or aperients. In fact, the treatment resolves itself into a treatment of symptoms.

X-ray therapy.—Rudnew and Krumberg instituted a new treatment by X-rays. The region of the spleen is irradiated for fifteen minutes with a fixed dose, filter 4 A. 1., tube 10 + 15, 2 milliampères.

Vaccine-therapy.—The therapeutic use of vaccines of dead organisms, prepared and administered according to Wright's methods, has been reported on favourably.

Autogenous vaccine.—In the Editor's experience, stock vaccines are of little benefit. The vaccine should be autogenous and prepared from the patient's organism isolated from blood-culture. In the latter instance, as a general rule, a considerable local reaction develops at the site of injection. Where blood-culture has been successful, the initial dose should be 50,000,000 organisms, and it should be progressively increased at three-day intervals, up to 200,000,000. In intractable cases the administration of vaccine in this manner certainly results in lowering of temperature and clinical improvement. Occasionally a pooled vaccine made from several different strains produces better results than does an autogenous one. According to modern conceptions of therapeutics, vaccine therapy is best combined with sulphonamide treatment.

Protein-shock therapy with non-specific protein (T.A.B.) vaccine, or *pyrifer*, has been found to cut the fever short by producing a febrile reaction with rigors (*see* p. 627).

Serum-therapy.—Sergent and Lhéritier produced an anti-melitensis serum by intravenous inoculation of cultures into a horse. They say it is effective if given in doses of 50 c.c. on three consecutive days; it is useful in chronic as well as in acute cases. An anti-melitensis serum is also prepared by Mulford, and is given in doses of from 50-100 c.c. It may be given by the intravenous route and repeated at twenty-four-hour intervals.

Sulphonamides.—Wilson discovered that, in the experimentally-infected guinea-pig, an animal which is specially susceptible, *sulphapyridine* has a definite action on *Brucella* organisms. The treatment with prontosil and other sulphonamides is being tried. Neumann and Petzetakis reported that their results were on the whole favourable. Prontosil is best given intramuscularly—5 c.c. of prontosil soluble, by injection for ten days, and simultaneously 1·5 grm. (3 tablets) daily by the mouth. After an interval of seven days, the oral treatment is recommenced for twenty days, and thereafter, if necessary, further treatment on the same lines is instituted. The results in children were specially favourable, and in these 4 tablets (2 grm.) are given daily for a week or ten days. Grouès further reported good results in eight cases from combined treatment with vaccine and sulphonamides. Large doses of sulphapyridine appear necessary, and the treatment should be persisted in: recent experience has shown that failure of sulphonamides is probably due to insufficient dosage, and adults should be given 4–9 grm. daily for courses of four or five days each—what is known as "Stoss-Therapie." Toxic sequelæ are methæmoglobinæmia and a morbilliform rash. Debono, (1938), in Malta, in severe cases, was quite unable to find any advantages from this treatment.

Fouadin.—Neumann from Malta reported favourably on a series of cases treated by intramuscular injections of fouadin. This is a trivalent antimony compound (pyrocatechin-disulphonic acid, *see* p. 825). Being non-irritating, it is given into the gluteal region in doses of 1·5 c.c. on the first day and 3·5 c.c. on the second, followed by 5 c.c. on alternate days. The maximum dose for women is 4·5 c.c. There is no pain at the site of injection, the drug is well tolerated, and no secondary effects have been observed. In a series of eight cases the temperature settled to normal in ten days.

The *diet* at first should consist of milk (in Malta, boiled); later, of broths and eggs and, if necessary, stimulants; but note that on sulphonamide treatment stimulants should be omitted. Solids must not be freely given during high fever or when the tongue is coated. If appetite is present, ordinary simple food may be taken. Lemonade or lime-juice should be given after a time; not merely as a pleasant, thirst-relieving beverage, but with a view to averting scurvy—not at all an improbable complication, if the dietary be too restricted over a long period. Feeding must be conducted with the greatest circumspection, avoiding overfeeding on the one hand and a low monotonous diet on the other. The tongue and the appetite are the best guides.

Exercise, travelling, and anything that tends to induce fatigue provoke relapse if indulged in prematurely; but a couch or chair in the garden is to be encouraged, weather permitting. The patient should rest for at least three weeks after the temperature has become normal.

Flannel clothing should be worn, and frequently changed if there is much sweating.

When possible, the subject of undulant fever would do well to avoid the endemic area for one or more years after recovery. In chronic cases a change of climate appears to be the only therapeutic measure of value.

Prophylaxis.—Malta and those Mediterranean ports in which this fever is endemic should be avoided by pleasure- and health-seekers during the summer. As a matter of precaution, in the endemic areas the drinking-water and food ought at all seasons to receive special attention. *All milk should be avoided, or sterilized by boiling,* and food dishes should be washed with boiled water. Laboratory workers must be careful in handling cultures of the bacterium; the accidental introduction of the organism into the conjunctival sac has sufficed to cause the disease.

The discovery that goat's milk is the principal medium through which undulant fever is communicated to man has led to very striking and important results. Unfermented cheese is a frequent source of infection and should be forbidden. In Toulon the disease has been traced to " fromage cervelle " made from the milk of sheep and goats.

On the recommendation of the Mediterranean Fever Commission, the use of the milk of the Maltese goat was interdicted for the naval and military forces of that island. Immediately, the incidence of undulant fever began to drop—in the Navy from an average of 240 per annum up to 1906 to 3 in 1910, and in the Army from a previous average of 315 per annum to 9 in 1907. In 1909 the health authorities in Malta were authorized to kill all goats whose blood or milk gave the *Brucella melitensis* reaction. The goat population of the island was consequently reduced from 17,110 in 1907 to 7,619 in 1910. Concurrently the fever incidence in the civil population fell from an annual average of 632 to 318 (Eyre). At present, as a result of the issue of condensed milk in place of goats' milk, the incidence of undulant fever has been greatly reduced in Malta (Stephens), while it has completely disappeared as a factor in the sick-list of the Army and Navy; indeed, no authentic case had been recorded during the three years preceding the outbreak of war (1939).

These facts suffice to indicate the direction preventive measures should take. It must be borne in mind that certain products of milk—e.g. cheese, butter—may communicate the germ, and, further, that infected goats may appear to be in perfect health and may milk satisfactorily.

The prevalence of infected animals is best determined by cultivating the organism from their blood or milk; failing this, serum reactions (p. 292) and Zammit's test are employed. The latter, which is known as the *lacto-reaction,* consists in diluting the milk to 1 in 20 and mixing it with a dense emulsion of *Br. melitensis* or *Br. paramelitensis*. The mixture is drawn up into the capillary tube and placed in the incubator for twenty-four hours, when any sedimentation present may be detected. It is better to heat the milk first to 56° C. for half an hour.

The proportion of infected goats has been estimated as follows:

Malta	50 per cent.
Algeria	3·4 „ „
Tunis	30·7 „ „
Marseilles	34·2 „ „

Zammit and Debono attempted to immunize the Maltese goat by dermal immunization. A filtrate of a broth culture, containing brucella organisms, is sprayed over the mammary region and into the mouth, and 1 c.c. is injected intradermally in four places. The treatment is repeated four times on alternate days.

Prophylatic inoculation.—Nicolle and Conseil conducted some experiments on man which seem to show that it is possible to immunize against undulant fever by subcutaneous injections of killed cultures of the organism; and similar results were obtained by giving 100,000,000 organisms by the mouth on three consecutive days, and again on the fifteenth day. These results were controlled by subsequently injecting cultures of living organisms; the controls in both cases developed undulant fever.

Dubois and Sollier have employed a vaccine of various strains of *melitensis* mixed with two strains of *abortus*. The complete vaccine made up of five strains contains 2,000,000,000 organisms per c.c. The first dose is 0·25 c.c. or 500,000,000; the second 0·75 c.c. or 1,500,000,000; the third 1 c.c. or 2,000,000,000. The full course of injections was given to 111 persons engaged in dealing with infected animals, and none of these developed undulant fever.

II. UNDULANT FEVER (ABORTUS Type)

Synonym. Abortus Fever.

Definition.—A definite variety of undulant fever in man produced by *Brucella abortus*, the organism of contagious abortion of cattle and swine.

History.—In 1878 Lehnert transmitted contagious abortion by intravaginal inoculation of pregnant cows with the vaginal discharges of aborting animals, and in 1896 Bang and Stribolt demonstrated small Gram-negative bacilli in the uterine exudate of infected cows, and isolated the organism in pure culture. This was later confirmed by Preisz (1903), Nowak (1908), McFaydean and Stockman (1909), and by MacNeal and Kerr in the United States in 1910.

In 1918 Miss A. C. Evans first showed the close relationship between Bang's bacillus and *Brucella melitensis*. Later she showed also that a close association existed between *Br. bronchisepticus*, an organism which produces a distemper-like disease in dogs and pigs. There appears also to be some connection with *B. tularense*, the organism of tularæmia.

In 1911 Schroeder and Cotton in the United States found that, as the result of injecting guinea-pigs with cows' milk, 14 per cent. were infected with *Br. abortus*. In 1914 Kennedy, in London, noted that agglutinins of *Br. abortus* (which was then thought to be *Br. melitensis*) were to be found in the blood serum and milk of London cows, and shortly afterwards this was confirmed by Bassett-Smith. These observations were extended by Wilson and Nutt in 1926, and extensive investigations on commercial milk were undertaken by Walker Hall, of Bristol.

In 1922 Bevan suggested that a type of undulant fever in Rhodesia, which had in recent years become very prevalent on farms where there were large numbers of cattle infected with epidemic abortion, was really caused by *Br. abortus*. He considered that the cow in this case was the source of infection. In 1924 Bevan's suggestions were amply confirmed by Orpen, who, on comparing strains of *Br. abortus* isolated from human cases and those derived from cattle, pronounced them to be identical; in the same year Duncan isolated in London *Br. abortus* from the blood of a patient from Rhodesia with undulant fever. From this time onwards it came to be recognized that sporadic cases of undulant fever occurring in European countries were of the *abortus* type. In 1923 Aublant, Dubois, Lafenêtre, and Lisbonne found that in France between 3,000 and 4,000 persons had suffered from undulant fever within a space of three years, and in the South-East Mediterranean area they attributed the prevalence of the disease to herds of sheep infected with *Br. abortus*, and the infection of man to drinking sheeps' milk. In 1925 the Editor described cases of undulant fever of the *abortus* type in England which undoubtedly were attributable to cow's milk. Madsen in 1928 found *abortus* fever widespread in Denmark. In 1926 Huddleson reported three cases of *Br. abortus* infection amongst students engaged in handling cultures in U.S.A., and in Germany the cases of five veterinary surgeons who contracted undulant fever from abortus-infected cattle were recorded. In 1931 over 1,545 cases were notified in the United States. Horning (1935) reported a severe outbreak of this fever in Connecticut in which *Br. suis*, the variety found in pigs, was the cause. Three cases were fatal. In this outbreak the cows had become infected with the *Br. suis* from the pig herd.

Geographical distribution.—Undulant fever of the *abortus* type in man has now been reported from the following countries: Italy, Canada, U.S.A., Denmark, Sweden, Germany, Holland, Switzerland, Austria, Poland, Palestine, South Africa, Rhodesia, New Zealand and Australia. In England the number of cases identified as *abortus* fever is growing yearly, and in 1933 over 140 were recognized and reported. Previous to this, sporadic cases had been reported from time to time and an attempt had been made to ascribe them to occasional drinking of goat's milk. Such cases were reported by Byam in 1918, by the Editor in 1927, and by Bamforth. Since that time the organism (*Br. abortus*) has been cultivated from the blood, urine and fæces in British cases.

Ætiology.—Traum (1914) isolated *Brucella* from a pig fœtus. *Br. suis* is transmissible to cattle and also to sheep, and Huddleson isolated the organism from the diseased testicle of a dog. Huddleson and Hardy, in Iowa, U.S.A., established that in that State *Br. suis* is the cause of many cases of *abortus* fever in man. There are many references to the concurrence of *Br. abortus* in the lesions of poll evil and of " fistulous withers " in horses. The organism is commonly associated with these lesions, but there is some difference of opinion whether they have not merely migrated to a suitable focus in which the filaria, *Onchocerca cervicalis*, is located.

In England, the cow is considered the main reservoir of infection. Menton (1937) found no evidence that goats or other animals are infected with *Br. melitensis* in England, although cows can be artificially infected, and the organism appears in the milk. It has been shown that *Br. abortus* can be recovered from 6·3 per cent. of cow's milk, and Elkington, Wilson, Cruickshank and others described outbreaks in schools due to consumption of unheated milk infected with *Br. abortus*.

Since the discovery of the porcine strain of *Br. abortus* (*Br. suis*) the tendency in America is to ascribe human cases to this source. Evidence in U.S.A. is to the effect that infection is acquired by meat packers from direct contact with pig carcases. Doyle found that a small proportion of sows in England is infected.

Differentiation of *Brucella abortus* from *Brucella melitensis*.—*Br. abortus* is usually somewhat larger than *Br. melitensis*, being from 0·4 μ to 0·6 μ in thickness, and varying in length from 0·8 μ to 2·5 or even 3 μ. The organism is remarkably pleomorphic; involution forms are unusual. *Br. abortus* can be isolated from the milk and uterine discharges of infected animals. Normal strains of *Br. abortus* of bovine origin cannot be grown in primary culture at the ordinary carbon-dioxide tension of the air, but to ensure growth it is necessary to raise the proportion of this gas to 5 per cent. or 10 per cent. by volume. These requirements diminish as the strain is propagated on artificial media. The simplest method of growing this organism is in a Bullock's jar in which cultures have been placed for incubation, adding a sufficient amount of pure carbon dioxide to produce the optimum concentration. In primary growth the colonies develop after inoculation in a zone 10–20 mm. below the medium. This behaviour is taken as evidence that *Br. abortus* is micro-aërophilic. After continuous subculture the organism can be grown under ordinary conditions. The porcine type, *Br. suis*, does not show the carbon dioxide growth requirements of the bovine type.

The organism grows best on glucose agar in which 2 per cent. glucose is added to a simple meat-extract agar medium set to reaction of *p*H 7·4, or in Fildes's medium. On potato slopes of alkaline reaction, differences in the growth character of *Br. abortus* and other organisms of the group may be found in week-old cultures; the former gives a uniform creamy-yellow growth, while *Br. melitensis* and *Br. paramelitensis* yield a greyish-chocolate or even black growth.

The reaction to dyes is important. The bovine *abortus* type is inhibited by the presence of thionin in suitable concentration, the porcine type by the presence of basic fuchsin, methyl violet, or pyronin. The *melitensis* type grows in the presence of all four dyes.

The formation of hydrogen sulphide from proteins or aminobodies containing sulphur is one of the most important biochemical reactions. The organism is grown on Staffseth's liver-infusion agar medium at a reaction of *p*H 6·6 and, after sowing, a strip of lead-acetate paper is introduced into the tube. After forty-eight hours' incubation a distinct blackening of lead acetate occurs in tubes sown with *Br. abortus*, while *Br. melitensis* produces no H_2S at all. On serological grounds, by means of the absorption of agglutinin method, the bovine and porcine *abortus* types may be differentiated from the *melitensis* type.

Br. abortus from cattle is grown best by seeding glycerin-agar slopes with the uterine exudate, and insulating them under a lowered pressure of oxygen or in the atmosphere of 10 per cent. CO_2. The best method of ascertaining the presence of *Br. abortus* in milk is by the cultural method. The milk is seeded with a liver extract peptone-agar in a CO_2 atmosphere. Alternatively, 0·5 c.c. of the milk may be injected subcutaneously into the hind leg of a guinea-pig, and the animal killed after three or four weeks: at the post-mortem examination the inguinal and lumbar lymph glands will be slightly enlarged and congested.

For isolation of *Br. abortus* from human blood, urine or fæces, the optimum for culture is a medium of *p*H 6·8, a temperature of 37° C., in an atmosphere of CO_2. When first isolated from the blood or the spleen, the organism may fail to show visible growth on the plates until after three days. Minute dew-drop colonies are then seen, which later become opaque, and are 3 mm. in diameter on the tenth day. Evans considered that 1 per cent. of glucose greatly enhances the vigour of the growth and that the new growth is obtained when liver is substituted for ordinary infusion-agar. For the first few generations of culture an atmosphere of carbon dioxide must be maintained, though this is unnecessary for later generations. Huddleson and Abell found that the growth of *Br. abortus* is inhibited by gentian violet, and that this can be used as a means of differentiation from *Br. melitensis*.

When cultivated from the blood the growth may be exceedingly slow. In one of the Editor's cases Wilson succeeded in demonstrating a growth on the twenty-first day of incubation, and Rainsforth (1933) recorded success after 60 days.

The isolation of *Br. abortus* from the fæces is no easy matter. Amoss and Poston succeeded by employing the following technique: a stool suspension is heated with an immune serum and clumps any organisms present in the sediment, which is then seeded into Teague's medium. Two plates are incubated in an atmosphere of air and two in a CO_2 atmosphere.

Br. abortus in cattle.—This organism produces abortion in otherwise healthy cows by causing inflammation of the uterine mucous membranes, of the fœtal membranes, and of the fœtus itself. The infection has become very prevalent in highly bred cattle herds when stable fed. both in England and in the United States.

The organisms occur first in the vaginal discharges as well as in the exudate from the uterus, while they are excreted in the milk of infected cows for many weeks and even months, so that *Br. abortus* is frequently found in commercial milk. In Washington 14 per cent. has been found infected, in Chicago 30 per cent., and in Dresden 32 per cent. When injected into guinea-pigs the infected milk produces small tubercle-like foci in the lungs, liver, and kidneys, and swelling of the spleen, which takes about seven weeks to develop. Sheep and pigs are less susceptible than cows. The symptoms of the affected cow are the escape of varying amounts of greyish-brown mucous discharge from the mucous membranes of the uterus and the chorion. It also affects the udders and probably spreads *via* the lymphatic channels. When a pregnant cow is infected the fœtus is expelled within eight to fourteen days. The fœtus itself shows infiltration of the subcutaneous and intramuscular tissues with *Br. abortus*; the calves are born covered with a purulent exudate and the chorion is converted into a leather-like substance, with buckling and wrinkling of the intercotyledonous parts of the membrane.

Apparently the bull may play an active part in conveying the infection, as the organisms have been found repeatedly in its genital organs.

The commonest time for abortion in cattle is from the fifth to the seventh month, and the incubation period lasts from one to thirty-three weeks.

When introduced into a fresh herd the disease usually spreads rapidly and assumes epidemic proportions; then it passes into an endemic state in which it remains for years. As a rule, the uterus frees itself quickly from the infection and *Br. abortus* is to be found in the udder, and in the supramammary and pelvic lymph glands, where it persists. From the udder the organism is excreted into the milk, and so it comes about that 34 per cent. of cows which give a positive agglutination reaction excrete *Br. abortus* in the milk, and may continue to do so for three years.

Under experimental conditions abortion may be produced in goats, guinea-pigs, rabbits, rats, and mice, and only rarely does it prove fatal. Guinea-pigs may be infected by rubbing cultures on to the depilated skin of the abdomen, and when these animals are thus infected artificially, they develop lesions simulating tuberculosis.

Pathology.—This is the same as in *Br. melitensis* fever. Occasionally, abscess of the spleen is observed. There is a general reticulo-endothelial hyperplasia of the lymph glands. Meningo-encephalitis with greyish-white tuberculations is reported in *Br. suis* infections in America.

Diagnosis of epidemic abortion in cattle.—The diagnosis of this infection in cows is made by serum agglutination, which takes place in a titre of 1 in 100 to 1 in 10,000, and the agglutinins can also be proved to be present in the milk of infected cows. For this purpose Bevan introduced the " abortoscope," which consists of a tube containing a standardized suspension of *Br. abortus*, closed by a cork to which is attached a double loop of thin wire coated with sterile paraffin. On the back of the tube is pasted a label marked " infected." Before use the suspension is thoroughly shaken up, and one loopful of blood from the animal to be tested is taken up in the wire, which is then returned to the tube and thoroughly shaken to mix the blood with the suspension. The apparatus is stood upright at room temperature so that in infected cases the suspension and the blood-cells settle down to the bottom of the tube, leaving a clear supernatant fluid through which the word " infected " can be read.

Generally speaking, in cows no attention is paid to an agglutination of a titre less than 1 in 50 in the serum. In a pregnant infected animal the titre gradually rises before abortion from 1 in 200 to 1 in 1,000, while a persistent infection of 1 in 400 or over indicates an udder infection.

The intradermal test or the abortin reaction in cattle.—This test, on the same lines as the tuberculin test, was introduced by MacFaydean and Stockman in 1909 in an attempt to introduce one based upon the hypersensitiveness of infected cows. Holtun (1928) described a double intradermal test in which 0·2 c.c. of a 5 per cent. phenolized suspension of *Br. abortus* heated to 65° C. for thirty minutes is twice inoculated into the same site at an interval of forty-eight hours, when the maximum infiltration of the skin is attained forty-eight hours after the injection.

ABORTUS INFECTION IN MAN

Diagnosis.—The agglutination test in *abortus* infections is much the same as in *melitensis*. An agglutination of 1 in 10 to 1 in 80, in the absence of clinical symptoms, indicates a past infection, while a titre of 1 in 100 or over, in the absence of clinical symptoms, probably indicates a latent infection, and a titre of 1 in 100, or over, in the presence of pyrexia and other symptoms of disease, may be considered as diagnostic of an active infection with *Br. abortus*.

The Editor has seen one case which showed a titre of 1 in 10,000, and other typical ones with a titre which never rose above 1 in 80. The agglutination test is best performed by the macroscopic method. A practical method of making a diagnosis by the agglutination test is by means of the " glutoscope," an apparatus devised by Bevan on the same lines as the abortoscope.

The intradermal test, or " *abortin* " reaction, is as useful in the diagnosis of *abortus* infection in man as is the parallel test in *melitensis* infections, and is performed in the same manner (*see* p. 291).

Diagnosis by blood-culture is the same as for *Br. melitensis*, and is successful in about 16 per cent. of cases ; (*see* p. 292). A certain amount of assistance may be obtained from the leucocyte count. There is usually a slight leucopenia with a relative increase in the lymphocytes. The average in seven cases of *abortus* infection under the Editor's care was leucocytes 6,800, with polymorphonuclears 48 per cent. and lymphocytes 48 per cent.

Symptoms.—Cohen divides *abortus* fever into five types: (1) the classical undulant; (2) the arthritic; (3) the abdominal; (4) the genital, of which orchitis is the chief feature; and (5) the "catarrhal jaundice" type. It is doubtful whether there are any signs or symptoms sufficiently obvious to enable a differential diagnosis between *abortus* and *melitensis* to be made from the clinical aspect alone.

On the whole, *abortus* infections run a much shorter course than those of *melitensis*. Some cases may be so mild that no obvious clinical signs are produced beyond the characteristic pyrexia. Atypical cases show slight fever, headache, listlessness, sometimes abdominal pain, sore throat and nocturnal sweating. As a general rule, however, prolonged pyrexial cases lasting many months, as in true undulant fever, are not common. On the other hand, *abortus* infections may be remarkably persistent over a year or more, but continued fever of over three months' duration is rare, though cases with multiple rigors and the characteristic undulatory febrile curves have been recorded. Some of the most severe clinical infections seen in England have been the result of infections contracted in the laboratory.

The spleen may be palpable as in *melitensis* infections, but is by no means invariably so. The premonitory signs of *abortus* fever are important; the infection may commence with pain behind the eyes and in the alveolar margins of the mouth. Unilateral or bilateral orchitis has been noted. There is usually an initial rigor which is followed by headaches, profuse sweats, and arthritic pains.

Abortion.—The great majority of pregnant women suffering from this disease do not abort, but the organism has been obtained from the vaginal contents in one such case. In Champney's series of 616 cases abortion occurred once only.

Hæmorrhage is somewhat unusual. It was noted in 5 per cent. of cases collected by Dalrymple-Champneys. Epistaxis was the commonest manifestation, but melæna, hæmoptysis, hæmatemesis, hæmaturia, menorrhagia, and bleeding from the gums may occur. Robinson (1938) has reported a case in which continuous oozing from the mouth and gums, associated with purpura, almost proved fatal.

Rash.—A papular or urticarial rash has been described, but occurs very rarely (Champneys).

Meningism is uncommon. There is stiffness of the neck, tremor of hands, slurring of speech, Kernig's sign and increased pressure of the cerebrospinal fluid. Meningitis has occasionally been reported and the cerebrospinal fluid may show increase in albumin and sugar content, but usually nervous symptoms are transient. One fatal case of meningo-encephalitis due to *Br. suis* has been described in the Mayo Clinic (1932).

Mild and chronic cases.—Alice C. Evans noted that in the United States chronic brucellosis is often characterized by vague symptoms—weakness, nervousness, insomnia, depression and irritability—and that in half the cases the agglutination reaction is negative. She therefore suspected this disease in cases of chronic ill-health in endemic areas. Mild or masked cases are also recorded. In these, ascertainable signs are absent, but small rises to 99° and 100° F. are seen to occur in a four-hourly chart, and usually only a low-grade agglutination with *abortus* in a titre of 1 in 20 can be demonstrated. There may be remarkably few symptoms, except, perhaps, headache.

Jaundice.—A form resembling infective hepatitis has been described.

Localizing symptoms.—Usually the arthritic pain and peri-arthritic effusions which are so characteristic a feature of *melitensis* infections are not so prominent in this type. It is, however, necessary to refer to two instances of isolated joint affections which the Editor has seen. In both, the shoulder-joint was affected, apparently due to localized *abortus* infection. Localized abscesses, and even fixation abscesses in bone, due to *Br. abortus,* have been reported, and constitute the condition known as "surgical brucellosis," described by Edwards (1937). In Iowa, U.S.A., osteomyelitis of long bones, including those of the wrist, has been described.

Treatment.—The treatment of *abortus* infections does not differ materially from that of the classical disease. As a rule, the symptoms are not so urgent and the span of the disease is shorter, so that drastic remedies are not usually required.

The cutting short of the fever by protein-shock fever-therapy has been found effective by S. Miller. He demonstrated that a fever of several months' duration can be terminated in a few days by three, or even four, intravenous injections of typhoid-paratyphoid organisms (or *pyrifer*[1]) in doses ranging from 50,000,000 to 150,000,000. The Editor also treated three cases with success, the fever being cut short by a protein-shock therapy two days after the isolation of the bacillus from the blood-stream. This may be combined with sulphonamides. Champneys reported that this was the most successful form of treatment in 25 out of 34 cases.

Fouadin has been tried, as in *Br. melitensis* infections, but the results have not been very striking (*see* p. 294).

Treatment by sulphonamides has been extensively used, and is based upon the experimental evidence of Wilson and Maier. They found that these compounds effectually extirpate the organisms (*Br. abortus*) in experimentally-infected guinea-pigs when administered for some weeks in large and almost sublethal dosage.

A summary of the results obtained up to November, 1938, in 13 cases from various sources (French, English and German), shows that the fever defervesced on an average in 15 days from the commencement of sulphonamide treatment, when these drugs were exhibited for a period of 17 days. Gaffney considered that, even when cases relapse, as they frequently do, on cessation of sulphonamide medication, the febrile remission will be shortened if treatment is resumed. Thomson (1938) found that *abortus*-infected patients can tolerate sulphanilamide up to 8 grm. daily. Bethoux, Gourdon and Rochedix described the successful treatment of one intractable case with intravenous injections of 20 c.c. of a 6 per cent. solution of soluseptasin. Pearson and Lewis (1940) gave a total dosage of 48 grm. of sulphapyridine in 18 days. A morbilliform rash following treatment is not serious and a fall of lymphocytes accompanying granulocytopenia is common.

The Editor has treated a series of three intractable cases with sulphanilamide. Two were cases of prolonged fever, the third of pyrexia associated with orchitis. On the whole, it may be claimed that the more manifest signs and symptoms of this infection are modified by sulphanilamide. Prontosil album was given in doses of 1·5 grm. daily, reinforced by injections of prontosil rubrum, 5 c.c. daily, for six days. In some cases it may prove necessary to inject the drug intramuscularly in order to obtain results.

Prophylaxis.—The prophylaxis of *abortus* infection in man is mainly bound up in the very difficult subject of the treatment and prevention of this disease in cattle, for the infection is undoubtedly contracted by drinking infected cows' milk by an individual susceptible to the disease. In herds of dairy cows, many carriers of the infection exist. There is a tendency for the organism to become located in the udder. Prophylactic inoculation and immunization of cattle by employing live cultures of *Br. abortus* has been extensively practised. In 1906 Bang reported that a certain amount of protection could be conferred upon animals by the intravenous injection of living cultures of *Br. abortus* some weeks before copulation, and this method was more extensively applied by Stockman in 1914 to non-pregnant cattle. In recent years a living strain of *Br. abortus* of low virulence has been employed in the immunization of cattle in America and England. These do not set up disease in cattle or render them infectious, and the organisms are not excreted in the milk. It is obvious that the remedy lies in the sterilization of *abortus*-infected milk, and this can be done by boiling or by pasteurization: thirty minutes at 140–145° F. will destroy the organism.

Since it was reported by Gilbert and Coleman that in 11 cases of human infection in Iowa the source had been traced to association with infected hogs, prophylactic measures have been taken in America in that direction.

CHAPTER XV

ENTERIC FEVERS
(AND BACTERIUM COLI INFECTIONS)

THE enteric group of fevers includes typhoid fever, due to *Bacterium* (*Salmonella*) *typhosum*, and paratyphoid fevers, due mainly to *Bact. paratyphosum-A* and *Bact. paratyphosum-B*. Paratyphoid-C fever has a somewhat different symptomatology (*see* p. 311). These organisms belong to what is now known as the *Salmonella* group, and the fevers caused by them were classified during the 1914–1918 war as " enterica."

History.—In the earlier half of the nineteenth century, typhoid and typhus fever were grouped together under the term " continued fever." The first clear differentiation of typhoid from typhus on clinical and pathological grounds resulted from the work of Murchison and Jenner (1855–62). Then came the discovery of the *Bact. typhosum* by Eberth in 1881, followed by that of *Bact. paratyphosum-A* (Brion and Kayser), of *Bact. paratyphosum-B* (Schottmüller), and of *Bact. paratyphosum-C* (Hirschfeld, 1919).

Geographical distribution.—Besides being the scourge of the young European in India, enteric is common enough in Japan, in China, in Cochin-China, in the Philippines, in Malaya, in Mauritius, in West and South Africa, in Algeria, and, in fact, wherever it has been properly sought. Thanks to protective inoculation with the triple vaccine (T.A.B.) and to sanitary measures, enteric fever during the 1914–1918 war was no longer the chief disease in our armies.

Prevalence.—Enteric fever is prevalent among young soldiers and recently-arrived civilians in the East, but, fortunately, liability to infection decreases with length of residence, owing apparently to acquired immunity. The well-known immunity of native races to typhoid is probably due either to mild attacks of the disease in childhood or to the immunizing effect of living in constant contact with typhoid infection. In insanitary native cities—Chinese, for example—where the European would almost surely contract typhoid, the natives have acquired a high degree of immunity. The typhoid and paratyphoid infections among Europeans in the tropics appear to be more virulent, and to cause a death-rate twice as heavy as that commonly observed in England. According to English statistics, the death-rate is given as about 1 in 8 attacked, but in India only recently the death-rate is stated as rather over 1 in 3.

Up to the early days of this century, typhoid in India used to kill more European soldiers than did cholera. Enteric fevers are apt to occur in camps in localities previously unoccupied by man. This has long been noted in India, while in Australia typhoid has occurred in the back country many hundreds of miles from human habitations.

Epidemiology and endemiology.—The essential factor in the propagation of enteric fevers in the tropics, as in temperate climates, is the individual who is passing enteric bacilli in his urine or fæces, or in both. He may be in the acute or the convalescent stage, or a " carrier." Three kinds of enteric carriers are mentioned by writers on this subject :

(*a*) The *acute carrier*, who passes enteric bacilli in the excreta for a short period after an attack of enteric fever. (*b*) The *chronic carrier*, who continues to pass enteric bacilli in the excreta for years, possibly permanently. Chronic carriers are more often women than men. The gall-bladder being the seat of a chronic infection, the carrier may be the victim of gall-stones and cholecystitis. (*c*) The *passive carrier* is one who continues to pass enteric bacilli in the fæces without having actually suffered from enteric fever.

The enteric carrier is a danger to the community, the degree of danger depending to some extent on his personal hygiene, but much more on the sanitary condition of the locality. Under an efficient water-carriage system of sewage disposal there is a minimum risk. Where the conservancy system—i.e. the dry closet—is employed, as in the tropics generally, the risk of infection is great. The modes of infection are: (1) directly from the infected person (patient or carrier) to the susceptible; (2) indirectly through water supply; and (3) indirectly by fly-carriage and contamination of food.

Bact. typhosum is practically world-wide. Paratyphoid-A fever is the most common form in the East (India), paratyphoid-B fever in Europe. During the 1914–1918 war the majority of enteric infections in France were paratyphoid-B, and the most extensive epidemic in the British and French troops was on the Gallipoli peninsula in 1915. But, relatively to former campaigns, cases of typhoid were few, the armies being almost completely protected by antityphoid inoculation. In the earlier part paratyphoid-B was the prevailing infection, while in the later phases the cases were almost exclusively paratyphoid-A. Paratyphoid-C fever, which resembles the fevers caused by *B. ærtrycke* and *B. suipestifer*, is widespread in British Guiana, but elsewhere has probably not the epidemiological importance of the other three (Giglioli).

Ætiology.—*Description of organisms.*—*Bact.* (*Salmonella*) *typhosum* is a Gram-negative motile rod, 2–4 μ in length and 0·5 μ in thickness. It is provided with numerous peritrichous flagella, and is very active when grown on artificial media. On these it thrives well, with growth resembling that of *Bacterium coli*, but less dense. In its biochemical reactions it differs considerably from that organism, and produces acid without gas-formation in maltose, glucose, and mannite, but causes no change in lactose, saccharose, and dulcite. It produces slight acidity in milk without clotting. No indol is produced in peptone water (*see* Table VII, p. 468). A new method of identifying strains of *Bact. typhosum* has been introduced by the discovery by Craigie and Yen of the type-specific typhoid Vi bacteriophages. By this technique it is possible to divide typhoid bacilli into a number of well-defined types. The phage type of a strain is a permanent character and the typing of the typhoid bacterium by these means gives reliable results. The paratyphoid bacilli A, B, and C resemble in their general morphological characters and staining reactions *Bact. typhosum*, but differ from it in their biochemical and immunity reactions. They also, like *Bact. typhosum*, are non-lactose-fermenters, but produce acid and gas in glucose, mannite, maltose, and dulcite, though they do not affect saccharose nor form indol in peptone water. Paratyphoid-A bacillus is weaker in fermentative power than B, and it produces permanent acidity in litmus milk, whilst B first produces acid, returning later to a permanent alkaline reaction. Their immunity reactions are also quite specific. Paratyphoid-C bacillus differs from B in its immunity reactions, and some bacteriologists might prefer to call it a serological race of *B. suipestifer*.

The portal of entry of the enteric bacilli into the tissues of their host appears to be the lymphoid masses forming the Peyer's patches and solitary follicles of the ileum. Here they cause a hyperplasia of the lymphoid tissues, followed at a later stage, in severe cases, by necrosis, sloughing and ulceration. The bacilli pass on to the lymphatic glands of the mesentery and posterior abdomen, which become enlarged. Finally, they enter the blood-stream. The period of bacillæmia coincides with the early febrile stage of the disease, and hæmoculture is successful in the majority of cases in which it is undertaken sufficiently early—i.e. while the temperature is still rising, or when it is continued without marked remissions. It is seldom successful after the first marked morning remission, especially in paratyphoid fever, or after lysis has commenced. The duration of bacillæmia varies greatly, depending on the severity of the case and duration of the pyrexia. It is, on an average, longer in typhoid than in the paratyphoid fevers. It is important, therefore, in the diagnosis of enteric fever, to set about hæmoculture as early as possible ; every day's delay diminishes the chance of success.

Alternately, it has been suggested that in enteric infections the invading organisms enter the blood-stream first (possibly through the tonsils), and that the intestinal lesions are secondary to the bacillæmia.

Although bacilli are eliminated in the fæces and urine, they cannot always be isolated from the excreta, even on repeated examinations, though the use of selective media has increased the proportion of successful results.

Pathology.—The most striking lesions found *post mortem* (in addition to the tissue changes common to all continued fevers) are : ulceration of the intestine, especially the Peyer's patches and solitary follicles in the ileum and jejunum ; enlargement and congestion of the abdominal lymphatics ; and enlargement and congestion of the spleen.

The most notable differences in the post-mortem appearances between typhoid and the paratyphoid fevers are : in paratyphoid fevers the intestines more frequently show no change, though they may be acutely inflamed throughout their length, the lymphatic tissue escaping ; and in paratyphoid fevers ulceration of the *large* intestine is relatively more frequent. Paratyphoid-C is in many instances a septicæmia, and deep metastatic abscesses due to this organism were described by Giglioli.

Post-mortem bacteriology.—The causative organism in enteric fevers may be recovered *post mortem* from the intestinal lesions, the enlarged abdominal lymphatics, the spleen, the gall-bladder, the heart's blood, and other tissues.

Symptoms.—The usual *incubation period* for all the enteric infections is about fourteen days, but it may be shorter than seven or longer than twenty-one days.

There is a wide range in the severity of the infections, and one clinical description cannot apply equally to all cases, from the mildest to the most severe. The variation is, however, more in the degree than in the nature of the clinical manifestations. After all that has been written, especially during the 1914–1918 war, on "atypical" enteric fever, this group remains, whether in inoculated or uninoculated patients, remarkably true to one type—which may be termed the "enteric type."

The typical *onset* is a gradual one, but it may, especially in paratyphoid fever, be sudden, with a shiver or even a rigor. Headache is the most constant early symptom, and is usually accompanied by malaise, anorexia, pains throughout the body and limbs, and insomnia. The tongue is coated, the mouth dry and uncomfortable, and the patient thirsty. There is a characteristic moist facies with cheek-flush, and a general apathy. These symptoms vary greatly, and in the mildest cases may pass undetected. Epistaxis is more common in typhoid than in paratyphoid. There may be pain or general uneasiness in the abdomen, but in mild paratyphoids the patient in many cases does not refer to that region. There may be diarrhœa from the commencement, or diarrhœa followed in a few days by constipation, or the patient may have obstinate constipation from the beginning. The temperature is invariably raised. It may mount step-ladder-like during the first week, or it may rise suddenly, to reach its highest point in the first 24–28 hours, and, after a period of continued fever, begin to remit in the morning and terminate by lysis.

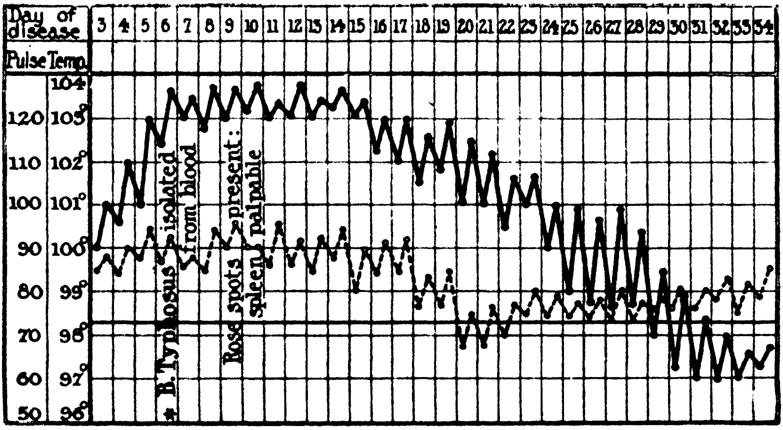


Chart. 16.—Typhoid fever, with graph of pulse-rate. (*Garrow.*)

A highly characteristic feature of all the enteric infections is the pulse, which is usually soft, often dicrotic, and relatively slow (Charts 16–18).

On physical examination, the abdomen may be found more or less distended, as in severe typhoid, or there may be little or no distension, as in the majority of paratyphoids. Splenic enlargement is practically constant, the organ usually being large enough, at some stages of the illness, for its lower pole to be palpable below the left costal margin. It may be felt in some cases on the second or third day, if the patient comes under observation so early, or not until the second or third week, or even later. In some cases it becomes palpable for the first time only after the temperature has become normal. Usually about the seventh to the tenth day, but it may be earlier or much later, " rose spots " appear. These vary considerably in number, size, shape, general characters and distribution. There may be only two or three on the abdomen, or the body and limbs may be covered, from the soles of the feet to the scalp. They are of a pale-rose colour, slightly-raised, round or lenticular, and fade on pressure. The more profuse eruptions occur in paratyphoid fever, especially paratyphoid-A. When the eruption is not of this profuse

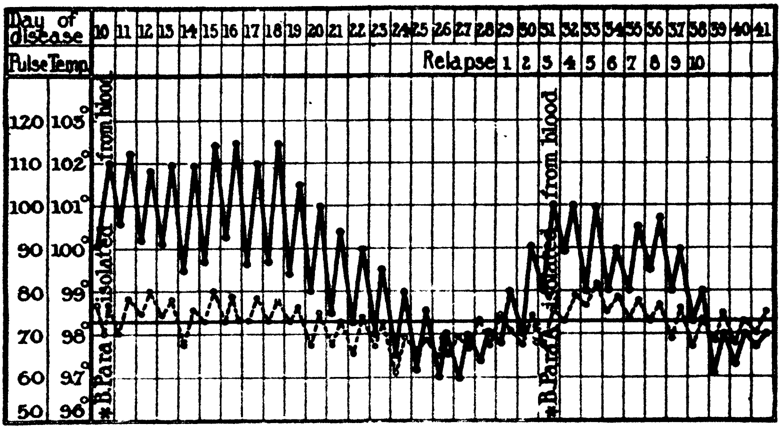


Chart 17.—Paratyphoid-A fever, with graph of pulse-rate. (*Garrow.*)

type its distribution is characteristic: 90 per cent. or more of it is on the trunk, between the levels of the iliac crests and the nipples. The patient usually coughs and has a certain degree of bronchitis. Certain features of *B. typhosum* infections, as they occur in Chinese, have been remarked upon by Wilkinson, Snapper and others. Multiple rigors are by no means uncommon. Hepatitis typhosa and jaundice, due to empyema of the gall-bladder, are frequent, whilst hæmorrhage, perforation and phlebitis are rare. The organism has been recovered from the cerebrospinal fluid in patients with meningeal symptoms. Atrophy of the skin and alopecia are common sequelæ, but the most dangerous complication is the lighting-up of long-standing pulmonary tuberculosis.

A patient with bronchitis who is more seriously ill than the bronchitic condition would explain should be suspected of typhoid.

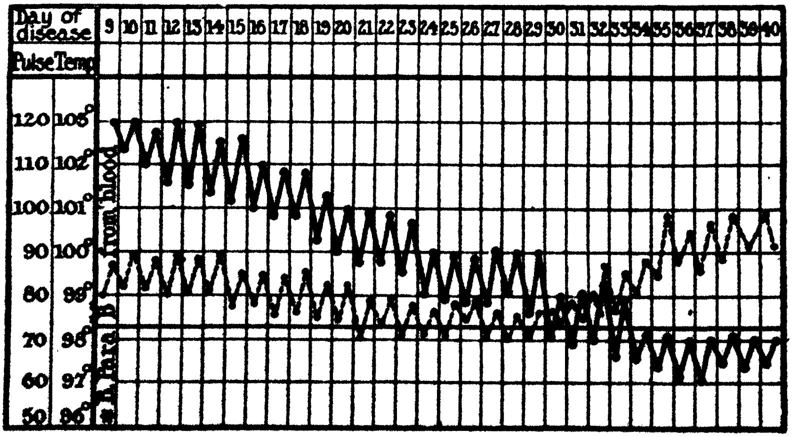


Chart 18.—Paratyphoid-B fever, with graph of pulse-rate. (*Garrow.*)

Diagnosis

Clinical diagnosis.—In the literature of enteric there is frequent reference to mild, atypical, abortive, and clinically unrecognizable forms; and it appears to have become the custom to leave the question of diagnosis to the laboratory. This was particularly so during the 1914–18 war, both at home and abroad, and it is greatly to be deprecated, because careful and repeated clinical scrutiny of these cases is more than ever necessary. In Garrow's opinion, the great majority can be correctly diagnosed clinically. While laboratory methods of diagnosis in the enteric group are undoubtedly important, undue value has been attached to certain bacteriological and serological findings, even to the extent of creating new clinical types of the disease to correspond to them. Far from being protean in their clinical manifestations, the enteric fevers are remarkably constant and true to type. The cardinal signs are five: (1) pyrexia of remittent type ending by lysis; (2) low pulse-temperature ratio; (3) characteristic toxæmia; (4) splenic enlargement; (5) eruption of rose spots. It is not pretended that this list exhausts the diagnostic signs and symptoms; but a consideration of these five signs will, in the great majority even of the milder cases, lead to correct diagnosis.

(1) *Pyrexia*—Continued pyrexia of remittent type, ending by lysis, may be regarded as a feature of every case of acute enteric fever (typhoid or paratyphoid). The pyrexia may be high or low, long or short, with remissions great or small. The onset of pyrexia may be gradual or sudden, and lysis may be slow or rapid, thus giving a great variety of temperature charts within the type; but there is no good evidence to show that the fever ever departs from this type. *Cases presenting the following features certainly should not be regarded as enteric:*

(*a*) Temperature is normal or subnormal throughout the entire illness (" apyrexial type of enteric ").

(*b*) Temperature reaches normal or subnormal at some period of the twenty-four hours on every day of the illness (" intermittent type of enteric ").

(*c*) Temperature shows perfect tertian or quartan periodicity throughout (" malarial type of enteric ").

(*d*) Temperature shows a series of short relapses of one to three days' duration, occurring at intervals of a few days (" trench-fever type of enteric ").

(*e*) The temperature ends by a genuine crisis.

Examples of all these so-called " types of enteric fever " will be found in the literature, the erroneous diagnosis having been based upon the unwarrantable bacteriological or serological finding.

(2) *Low pulse-temperature ratio.*—One of the most valuable diagnostic points is the slowness of the pulse in relation to the pyrexia. The normal pulse-temperature ratio may be tabulated as follows:

Pulse	**50**	**60**	**70**	**80**	**90**	**100**	**110**	**120**	**130**	**140**
Temperature	**96°**	**97°**	**98°**	**99°**	**100°**	**101°**	**102°**	**103°**	**104°**	**105°**

In enteric fever the pulse is, as a rule, 20, 30 or 40 beats per minute slower than thus indicated. For example, it is common to find an enteric patient with a temperature ranging about 103° to 104° F. and a pulse of 90 beats per minute, or it may be even slower. If the pulse is recorded graphically in red ink alongside the temperature curve in black, a very striking clinical feature of great diagnostic significance is clearly brought out.

(3) *Characteristic toxæmia.*—There is something very characteristic in the general appearance, facies, and decubitus of the enteric-fever patient. His disease may in many cases be confidently diagnosed by a glance. He has a dull, heavy, toxin-laden appearance in the early acute stage, with a moist face and flushed cheeks. The experienced clinician at once recognizes the difference between this and the toxæmia of, say, malaria or relapsing fever. In the mildest paratyphoid infections there is little or nothing of this toxic appearance, whilst some infections other than enteric are accompanied by a general toxæmia closely resembling it. Nevertheless, this sign, to the experienced physician, when taken in conjunction with the others, is of diagnostic significance.

(4) *Splenic enlargement.*—As some degree of splenomegaly is practically invariable, this sign is of considerable value in making a diagnosis. Unlike the majority of tropical splenomegalies from other causes (malaria, kala-azar, etc.), the enlargement is acute, so that, even when superadded to a spleen already enlarged from malaria, it has certain exceptional features of diagnostic significance. For example, the acutely enlarged spleen of enteric is tender. On palpation, the edge is seldom more than two fingers' breadth below the costal margin, often not so much ; and the enlargement is of comparatively short duration. The spleen may only be palpable for two or three days, and then recede. It may become palpable as early as the second or third day of fever, or not till the second or third week, and it may remain enlarged long into convalescence.

(5) *Rose spots* may appear in the first week, but more often in the second, and tend to come in crops. They may not appear until the temperature is normal. In warm climates, many European skins are apt to show spots more or less like those of enteric fever, as the result of mosquito-bites and of inflammation of hair follicles or sweat-glands. Great care must be taken in discriminating between the true spot and these "pseudo-rose spots." There are many European skins which, in spite of the trying conditions of the tropics, remain free from blemishes of this sort, and in these cases the recognition of the typical spots is relatively easy.

Summary of clinical diagnosis.—Every undiagnosed fever in the tropics should be regarded as a possible case of enteric fever and closely observed clinically, at the same time that bacteriological and serological investigations are being carried out and Marris's atropine test is applied. While valuable clinical evidence may be obtained from occasional signs, such as epistaxis, pea-soup stools, abdominal distension, and hæmorrhage from the bowel, the diagnosis should rest in the great majority of cases upon the presence or absence of the five cardinal signs. Any case presenting the first, second, and third signs should be treated as enteric (whether the diagnosis is supported by laboratory findings or not) until some other definite diagnosis is made. No case which does not show the first, together with at least two of the remaining four cardinal signs, should be definitely regarded as enteric. Five types of temperature chart have been described, any of which excludes enteric. These, however, imply that the case has had its temperature recorded from the outset, which is not often possible. In the majority of cases of active enteric fever, all five signs are present at one or other stage of the illness.

Finally, it should be remembered that, for every case of enteric fever which imitates some other disease, there are at least a score of cases of other diseases imitating enteric (malaria, trench fever, phthisis, liver abscess, syphilis, etc.).

Paratyphoid-C.—This, as observed by Giglioli in British Guiana, although essentially a " fever " producing a temperature chart not unlike those of other paratyphoid fevers, is a septicæmia, and the intestinal tract may not be specially involved. Complications such as arthritis, abscess formation and cholecystitis are common, and fixation abscesses from intramuscular quinine injections may occasionally contain a pure culture of the bacillus. There appears to be a special connection between paratyphoid-C infection and malaria. The mortality of Giglioli's series of 92 cases of definitely diagnosed paratyphoid-C infections was 38 per cent. Probably a great number of abortive and mild cases passed unobserved. A few cases have been reported in the army in India during recent years.

Bacteriological diagnosis of " enteric " (*see* p. 1014).—(*a*) *Hæmoculture* is unquestionably the most satisfactory method of diagnosis ; it should be employed, wherever the necessary facilities are available, in every case of undiagnosed pyrexia in the tropics as soon as a blood-film is found to be free from malaria parasites. A successful hæmoculture furnishes the only conclusive evidence that the patient is suffering from active enteric fever, and can hardly be said to be open to fallacy. Unfortunately, however, the usefulness of the method is limited by the short duration of bacillæmia. In many cases which are undoubtedly enteric, negative results are obtained because hæmoculture has been attempted too late. Recent experience has shown that culture from the *blood-clot* gives the highest percentage of positive results. Culture of material obtained by sternal puncture (medulloculture) has been shown to be useful in paratyphoid B infections, and in China it has proved to be more practical and reliable than blood culture.

(*b*) *Culture of excreta.*—Urine and stools should be plated when blood-culture has failed, and this should be repeated during convalescence to determine whether the patient is free from infection. Bacilluria occurs after the fourteenth day in about 25 per cent. In about 75 per cent. of cases, and, under modern conditions, by employing the brilliant green enrichment method, tetrathionate broth or Wilson and Blair's agar medium for concentrating the typhoid and paratyphoid bacilli, cultivation of the organisms from the fæces in all stages is now successful. Glass and Wright (1937) showed that this method gave a high percentage of results, especially in the early stages ; so that during the first two weeks it is more likely to be successful in diagnosis than the Widal reaction. Some positive findings from culture of excreta are open to fallacy. The case may be one of an enteric carrier suffering from some illness other than enteric—e.g., malaria or trench fever. The detection of carriers can only be effectually carried out in a fully-equipped laboratory; at least seven separate and consecutive bacteriological fæcal tests are necessary.

Serological diagnosis.—One of the simplest and most reliable laboratory tests is the examination of the blood-serum of suspected enteric-fever patients for the specific agglutinins of the enteric bacilli—the *Widal reaction*. When carefully applied by reliable methods in *uninoculated patients*, it gives a correct diagnosis in the great majority of cases. Assuming correct technique, the only possible fallacies are that a positive Widal reaction may result from a *previous* attack of enteric, and that a negative result may occur in the early stage of an attack of enteric. If a negative finding is obtained in face of clinical data pointing to enteric, the test should be repeated, on several occasions if necessary. A few cases of enteric, especially paratyphoid-A, may fail to develop agglutinins and continue to give a misleading negative Widal reaction throughout.

The serological diagnosis of the enteric fevers in *inoculated patients* gave rise to much conflict of opinion during the 1914–1918 war. Inoculation produced in the blood-serum specific agglutinins indistinguishable qualitatively or quantitatively from those produced by infection. The mere recognition of these specific substances, therefore, had not the diagnostic significance in the inoculated that it has in the uninoculated. It had, until the recognition of H and O agglutinins, hardly any diagnostic value. It was demonstrated, however, by Dreyer and his co-workers, and by others, that if an accurate estimate of the agglutinin content of the serum was made early in enteric fever and repeated at intervals of a few days, there is a steady rise to a maximum, followed by a slower fall. Dreyer and Walker stated that this maximum usually occurred between the eighteenth and twenty-first days of the illness, and almost invariably between the sixteenth and twenty-fourth days. They therefore gave to the latter period the name "period of expectation." To this agglutinin fluctuation they attached a significance practically pathognomonic. The agglutinin fluctuation, when considered in relation to the clinical data, though useful, cannot now in itself be regarded as conclusive.

In uninoculated patients differential diagnosis is obtained by agglutination tests with the patient's blood-serum against emulsions of the four organisms. Each infection produces its specific agglutinin, and the phenomenon of co-agglutination does not often interfere with the diagnosis. In patients who have been inoculated with triple vaccine, differential diagnosis is considerably complicated. The response may be specific, but frequently two or all three agglutinins may show variations (*see* Appendix, p. 1015). It is still held, as stated above, that a progressive rise in agglutinin titre to one specific antigen denotes active infection; but it must be stressed that a rise in immune bodies (or residual-anamnestic agglutinins) may be stimulated by other pyrogenic infections, such as malaria.

Felix and Pitt have shown that strains of *Bact. typhosum* of high virulence have the property of being relatively inagglutinable by sera which contain a high titre of antibody acting on the "O" somatic antigen, which is one of the most characteristic components of the "smooth" strains, and this inagglutinability is associated with the possession of additional antigenic constituents which can be differentiated from the ordinary "O" antigen. Thus, mice immunized with a vaccine containing the additional antigen in an active form are rendered resistant to injection of highly virulent bacilli. This antigen is separate and distinct from the " O " and " H (flagellar) " antigens of *Bact. typhosum* (and this applies to the paratyphoid group) and renders the " O " antigen resistant to the " O " antibody. The symbol Vi (referring to virulence) is suggested for this antigen and the corresponding antibody. This Vi antibody is demonstrable by agglutination and absorption tests, and its *in vitro* titre is comparatively low. Active and passive immunization disclose the powerful protective action of the Vi antibody. The " O " antibody also neutralizes the *endotoxin* of *B. typhosum*, whereas the Vi and " H " antibodies are incapable of this action. Perry, Findlay and Benstead showed that virulence for mice, rather than mere smoothness in the usually accepted sense, offers the best criterion of the immunizing power.

The symbols " H " and " O " stand for German terms which denote respectively cultures which spread or which remain circumscribed. There are two main types of *typhoid bacilli :* the V form which contains " H," " O " and Vi antigens, and the " W " form which does not contain Vi antigen. Craigie discovered a method of typing typhoid bacilli by specific bacteriophages, of which no less than 13 are now recognized, and by the use of which it is possible to detect the source from which the organisms have been derived.

The original claim made by Felix that only " H," but not " O " agglutinins are formed as the result of passive inoculation, and not as the result of infection by living organisms, appears to be incorrect, since both may appear, and also Vi agglutinins, as the result of inoculation with dead organisms. It is held that " H " agglutininogens are heat-labile and are also destroyed by alcohol, while " O " agglutininogens are heat-stable.

Atropine test.—This test, devised by Marris, depends on the fact that in health, or disease other than enteric, a hypodermic injection of atropine sulphate ($\frac{1}{33}$ gr.) is followed by a rise in the pulse-rate amounting to at least 15 beats per minute, whereas in enteric no such rise follows. Should there be any rise at all, it will be less than 14 beats per minute, but often there is none.

The patient should lie horizontally and remain at perfect rest. He should not be tested until at least one hour after the last meal. The pulse-rate should be counted for at least ten minutes, and then gr. $\frac{1}{33}$ of atropine should be injected over the triceps region. After an interval of twenty-five minutes the pulse should be counted again, minute by minute, until it is clear that any rise which may have followed the injection has begun to pass off. The period of the disease during which the test is most reliable is said to be the fifth day to the end of the second week.

Auxiliary methods of diagnosis.—The diazo-reaction in the urine is useful, but may be present in malaria. Russo's methylene-blue test is said to be more conclusive, as it is absent in malaria.

Differential diagnosis.—The abdominal pain of enteric may be mistaken for *appendicitis*, but the matter may easily be settled by a leucocyte count, which in the former shows a leucopenia with a relative lymphocytosis, and in the latter an active leucocytosis. *Bacterium coli infections* may resemble enteric. *Typhus* is notably difficult to distinguish in its earlier phases, though the leucocytosis in that disease may be of considerable assistance.

It must not be forgotten that enteric fever may co-exist with some other acute infection such as malaria.

Diagnosis of typhoid from paratyphoid.—There is no *clinical* feature to distinguish the typhoid and paratyphoid infections from one another with any certainty. Yet there are general points in which they differ. Thus, typhoid fever (*Bact. typhosum*) is the most severe of the group, with the highest case-mortality (15 per cent. or over, as compared with 2 per cent. or less for the paratyphoid fevers). The typhoid patient looks more toxic; his temperature is, on an average, higher, with smaller morning remissions; he more frequently shows evidence of gross intestinal lesions (ulceration) e.g. diarrhœa, hæmorrhage, abdominal distension, perforation. The rash is more scanty and the individual "rose spots" are smaller and slightly darker than in paratyphoid. There is greater loss of flesh in typhoid than in paratyphoid. Paratyphoid is characterized by a milder toxæmia. There is seldom abdominal pain or distension, and constipation is the rule. Hæmorrhage and perforation are rare. The rash is more profuse and may cover the entire body and limbs.

But typhoid is frequently of the very mild type, and, on the other hand, paratyphoid may be like the worst typhoid. It is therefore quite impossible to say on clinical grounds alone whether any individual case is one of typhoid or paratyphoid.

Still less is it possible to arrive at a differential diagnosis on clinical grounds between A, B, and C cases of paratyphoid, although here again, over a series of cases, distinct clinical differences can be noticed. For example, relapses in paratyphoid-A are more frequent than in any other of the enteric infections, and less frequent in paratyphoid-B. Paratyphoid-A is, on an average, of longer febrile duration than paratyphoid-B, but the latter, on the other hand, is more often followed by jaundice, thrombosis and suppurative complications.

Treatment.—There is no generally accepted specific therapy for enteric fever; nor is there any drug which is known to exercise an active influence over this disease. In these circumstances it is best to confine treatment to providing the best hygienic conditions, good nursing, and careful dieting. All that the great majority of mild paratyphoid cases require is a soap-and-water enema every other day to relieve the constipation. Milk should be the diet while the patient is febrile; thereafter custard, milk pudding, soup, fish, and meat diet. The diet should contain about 70 grm. of protein a day, with a caloric value of 2,500–3,000. Water should be given freely. Purgative medicines should be avoided. The care and cleanliness of the mouth and teeth are important.

In cases marked by great toxicity with high temperature (over 102·5° F.) and no morning remissions, tepid sponging is beneficial; in the worst cases the cold bath or ice pack may be used. The temperature of the water should be between 70° and 85° F.; a tub of canvas and mackintosh sheeting may be improvised. Food may be given as a stimulant after the bath. The rectal temperature should be taken immediately on removal from the water, and again three-quarters of an hour later.

Felix's antiserum treatment.—Working on his observations on the virulence of smooth strains of *B. typhosum* towards the "O" antibody and the Vi antigen which is definitely associated with virulence, Felix (1935) produced an efficient antiserum from horses by injecting the Vi antibody. The therapeutic effects of this serum have been tested in a number of cases in Palestine and in Dublin. The results so far obtained are encouraging, for they indicate a favourable action on the toxæmic manifestations of the disease and the pyrexia. The dose is 25 c.c. of serum on three successive days. In very severe cases this dose may be doubled. McSweeney reported the recovery of a dangerous relapse treated in this manner, as well as of a child of four years with typhoid meningitis in which the bacillus had been recovered from the cerebrospinal fluid.

It is necessary that the serum should be injected early in the course of the disease. Cookson and Facey (1937), in a report upon 73 cases, noted in 73 per cent. an improvement within forty-eight hours of the injection ; in a further 10 per cent., some benefit accrued after a few days' interval, and in these it is possible that the action of the serum was delayed. The mortality of patients treated in this manner was 9·5 per cent. Robertson and Yu in Shanghai confirmed these results in 52 severe cases of typhoid. Using a concentrated serum, the standard dose employed for an adult was 50 c.c. administered intramuscularly. Thirty cases responded by a drop in temperature and a decrease in toxic symptoms. In 15 cases no appreciable effects were observed.

Metallic tin.—Reitler and Marberg (1943) in Palestine showed that metallic tin exerts a slow bactericidal action on *Bact. typhosum* : a preparation of tin stearate and colloidal metallic tin has a favourable action in typhoid fever, decreasing the death-rate to 3 per cent. in 100 selected cases, whilst the average death-rate of a control group of 428 patients was 8·2 per cent. They believed that these effects are due to the coincidence that the drug and causative organism have a common site of accumulation in the lymphatic nodes. It is also effective in the carrier state. Each tablet contains 0·012 grm. of tin. The drug is given daily for ten days. Adolescents receive 16 tablets on the first day ; 8 tablets daily for the following 9. The dose above 15 years of age is 20 tablets on the first day ; subsequently 10 tablets for the following 9 days. In cases of concomitant pneumonia the combination of tin and sulphapyridine causes severe vomiting ; therefore the latter should be given by the parenteral route.

Vitamin C in treatment.—Intravenous injection of this vitamin, together with extracts of the suprarenal glands containing the hormone, were advocated by Hartmann and others. The cortical hormone is *Eschatin* (P. D. & Co.), which contains only a negligible quantity of adrenalin. The vitamin C preparation is known as Cébion (Merck). Intravenous injection of suprarenal cortical extract is commenced in doses from 5–20 c.c., together with 500–1,000 mgm. of vitamin C. The two products are injected together.

Mandelic acid.—Basing his premises on the biological relationship between *Bact. coli* and *Bact. typhosum*, Kleeberg advocated the routine use of mandelic acid which he claims influences the course of the fever.

The management of convalescence demands care, especially in paratyphoid-A infections, and the return to solid diet should be postponed until the temperature has remained normal for at least ten days.

For the bacilluria associated with enteric, urotropine (hexamine) in doses of gr. 10 three times a day usually acts, though the sulphonamides—sulphapyridine especially—are proving more efficacious.

In hæmorrhage, all fluids should be stopped for at least 48 hours, and sufficient morphia injected to keep the patient at rest. Though a very large amount of blood may be lost without causing a fatal result, yet, when feeding is recommenced it should be proceeded with very carefully. As a general rule, one large hæmorrhage is less serious than a number of smaller ones. When bleeding has ceased, a subcutaneous infusion with saline up to 1¼ pints may be permitted, and this may be repeated later should no further hæmorrhage occur. Blood transfusion has been employed with advantage and appears to arrest the hæmorrhage. It is advisable, should hæmorrhage be suspected, to give 30 gr. of calcium lactate three times daily; some make a practice of doing so from the sixteenth to the twentieth day of a typhoid fever, and from the fourteenth to the eighteenth day of a paratyphoid. In thrombosis, sodium citrate is indicated.

Prophylaxis.—*Anti-enteric inoculation* has been conspicuously successful, as shown by the statistics of the American Army, and of the British Army in India. During the 1914–18 war the vaccine was modified by the introduction of *Bact. paratyphosum-A* and *-B*, and the statistics furnish conclusive evidence of the efficacy of this measure of prevention, not only in lessening the incidence, but also in modifying the disease or diseases. Therefore, everybody proceeding from a country such as England to the tropics or subtropics should be inoculated with two doses of triple vaccine (T.A.B.), and should be re-inoculated every three years subsequently with one dose, so long as he remains in a country where enteric is prevalent.

The typhoid vaccine, as originally introduced, caused a considerable reaction, but by better methods of preparation and dosage in recent years the reaction has been mitigated. The official vaccine contains 1,000 millions of typhoid bacilli, 750 millions of paratyphoid-A, and an equal number of paratyphoid-B, to each c.c. Two doses of 0·5 c.c. and 1 c.c. are given at an interval of ten days. The reaction in the majority of instances is slight. Occasionally, however, cases of persistent pyrexia with severe local symptoms, malaise, and headache are met. In countries where paratyphoid-C is prevalent a tetravalent vaccine should be employed.

Preparation of the vaccine.—The organisms are grown upon trypsin-agar, washed off in saline and killed by heat. The vaccine is then standardized by combining the various bacterial suspensions in their appropriate proportions. The final emulsion is preserved by the addition of 0·4 per cent. lysol.

Statistics.—During the South African War, when prophylactic inoculation was incompletely practised, there were 60,000 cases of enteric, with 8,227 deaths. With millions of men under arms during the first two years of the 1914–18 war, only some 4,000 cases of enteric were reported from France, with a case-mortality of less than 2 per cent. In the Navy, Bassett-Smith's statistics record an incidence of only 144 cases of enteric during the year 1917, of which 8 occurred in inoculated and 136 in uninoculated individuals.

The American Army shows much the same figures; for two years, 1917–19, among an average strength of over two million men, there were only 213 deaths from enteric, and it is calculated that, had typhoid prevailed in the same proportion as in the uninoculated troops in the Spanish-American War, the death-roll from this cause would have been over 60,000.

In the Royal Air Force a dissolved T.A.B. vaccine is used, the solvent being sodium lauryl sulphate. This vaccine is prepared by Glaxo Laboratories. When injected it [illegible] rise to reactions considerably milder than did that formerly employed, though it appears to produce an equal quantity of bactericidal bodies in the blood of inoculated persons. No definite correlation could be found between the H and O agglutinin titre and the bactericidal potency of the human sera tested.

The problem of enteric infections among natives employed in the Rand Gold Mines has given rise to a considerable degree of anxiety. In seven years (1930–37) the number of cases was 6,611, and the " carrier problem " among these people is very serious. In December, 1936, inoculation with *endotoxoid* vaccine was initiated, with a great diminution in the number of cases of " enteric " notified. The prophylactic inoculation against typhoid and paratyphoid fevers has been recommended by the Transvaal Mines Medical Officers' Association.

Vi antigen.—Recent work by Felix on typhoid and paratyphoid antigens has shown that formalin (commonly used for killing cultures) has a definite deleterious action on " O " antigen which is concerned with typhoid immunity, whereas heating to 60° C, or higher, leaves this antigen intact. Another antigen of typhoid—the Vi antigen—which Felix maintains is connected with typhoid immunity, is destroyed by heating to 60° C, or by formalin, but can be preserved by killing the bacteria with 75 per cent. alchohol.

The new Vi alcohol-killed vaccine is now under trial. The vaccine retains its power after storage in the cold for at least nine months. Felix, Rainsford and Stokes compared this Vi vaccine (T.A.B.) with ordinary heat-killed T.A.B. and T.A.B.C. vaccine from various sources. Two marked differences were found between groups of subjects inoculated with the two types: alcohol-killed and preserved vaccines stimulated demonstrable Vi antibodies in a relatively high proportion, whereas the Vi antibody response to ordinary vaccines is negligible. No significant difference in O antibody response was observed. Reactions produced by alcoholized vaccines were milder than by the ordinary method.

Felix's Vi Vaccine contains:
1,000 million *Bact. typhosum.*
500 „ A, B, C. per. c.c.

Dosage.	*1st. dose.*	*2nd. dose.*
Adult males	0·25 c.c.	0·5 c.c.
„ females	0·2 „	0·4 „
Children		
16–18	0·2 „	0·4 „
13–15	0·1 „	0·2 „
9–12	0·05 „	0·1 „
under 8	0·05 „	0·05 „

Interval between injections: three weeks; revaccination advisable one year after primary immunization. The injections should be made as late as possible in the day.

Measures to avoid infection.—The most effective method for avoiding enteric infection is the water-carriage system of sewage-disposal. This, however, is not general in the tropics, so that other methods must be considered. They are: (*a*) detection of enteric carriers and their control, especially in relation to the selection, distribution and cooking of food; (*b*) protection of water supplies; (*c*) extermination of flies, and preventing them from access to excreta and refuse on the one hand, and to food for human consumption on the other.

ENTERIC-LIKE FEVERS

Septicæmia due to *Bacterium fæcalis alkaligenes* and other organisms.—During recent years a series of mild pyrexias, of either remittent or intermittent type, has been proved by Hirst and others to be due to infection with *Bact. fæcalis alkaligenes* (Table VII, p. 468). It is a common inhabitant of the intestinal canal, where it is not definitely known to exert any pathogenic action. The fever it gives rise to in the blood-stream may last from two to fifteen days. There is an evening rise with marked morning remission. The symptoms resemble those of a mild enteric, the pulse is slow in relation to the temperature, and the tongue is slightly furred. In some cases the patient's serum clumps the homologous organism in a dilution of 1 in 50.

In outbreaks of food-poisoning or "ptomaine poisoning," which occur from time to time, bacilli of the Salmonella group, *Bact. enteritidis*, *Bact. ærtrycke* and *Bact. suipestifer*, have been isolated from the blood-stream. The fevers they produce have many features in common with enteric. They differ in the suddenness of the onset, with rigors, the accentuation of the gastro-intestinal symptoms, the short duration and rapid termination of the fever. *Bact. ærtrycke* resembles *Bact. paratyphosum-B* in its biochemical, but may be differentiated by its serological reactions.

Bacterium coli infections.—Infection of the bladder and urinary tract with *Bact. coli* is frequently met in both sexes in the tropics. Should the organism enter the blood-stream it may give rise to a prolonged intermittent pyrexia resembling enteric. *Bact. coli* septicæmia and pyæmia may be a terminal infection in debilitated natives, especially as a sequel of bacillary dysentery; in these cases the organisms gain entrance to the blood-stream through the intestinal lesions, and, becoming arrested in the glomeruli, give rise to multiple minute abscesses in the cortex of the kidneys, from which they escape intermittently and appear in the urine (Fig. 53). The condition, which was first described in Egypt by Enright and the Editor, has now been found fairly commonly as a sequel of bacillary dysentery in the Middle East. The general condition of the patient, the stupor and the intoxication, may resemble those of enteric, but the onset is generally sudden, with headache, and acute pain referred to both kidney regions. Usually vesical irritation is absent. The tongue is thickly furred; rigors are numerous and accompanied by profuse sweats. The organism may be recovered in pure culture from the blood-stream during the rigors, as well as from the urine by ureteric catheterization. The acute attacks are apt to be confused with those of malaria. This form of *Bact. coli* infection is amenable to sulphonamide (sulphapyridine and sulphadiazine) treatment.

Pyelitis.—It was formerly considered that the anatomical relationship of the renal pelvis to the colon determined the frequency of infection, especially of women, but Leishman (1939) found that looseness of the bowels was the most frequent determining factor, suggesting an ascending infection. The symptoms may commence with a rigor and a dull aching pain in the loins which is increased on pressure. Micturition may be frequent, and sometimes a large and tender kidney may be palpated. The results of the inflammation are soon seen in the urine, which contains albumin, pus cells, and sometimes even blood. *Bact. coli* is present in large numbers, especially in the first specimen of urine passed during the day. Differentiation from malaria, which it may closely resemble, may be necessary. *Cystitis* with pyrexia and acid urine may also be due to *Bact. coli* and is very apt to occur as a sequel to any debilitating tropical fever, especially in enteric infections. It is always necessary to consider this possibility. *Bact. coli* infections of the urinary tract are quite commonly engrafted upon some other more serious infection, such as tuberculosis, and may mask the original picture of this disease. The possibility of ascending infection of the ureters from a long-standing prostatitis or urethritis in the male must not be ignored. In women this may be a sequel of miscarriage or parturition.

Treatment.—The treatment of *Bact. coli* infections of the urinary tract, which is so important in tropical practice, has been placed on a much surer and more satisfactory footing by modern discoveries in therapeutics. It was found that the excretion of ketone bodies in the urine destroyed the greater number of the *Bact. coli* organisms, and this led to the application of *mandelic acid*, which produces similar changes in the urine. Mandelic acid is related to β-hydroxybutyric acid and produces a high degree of acidity—pH5—in the urine, together with acetone. A methyl-red indicator is employed to estimate the hydrogen-ion concentration.

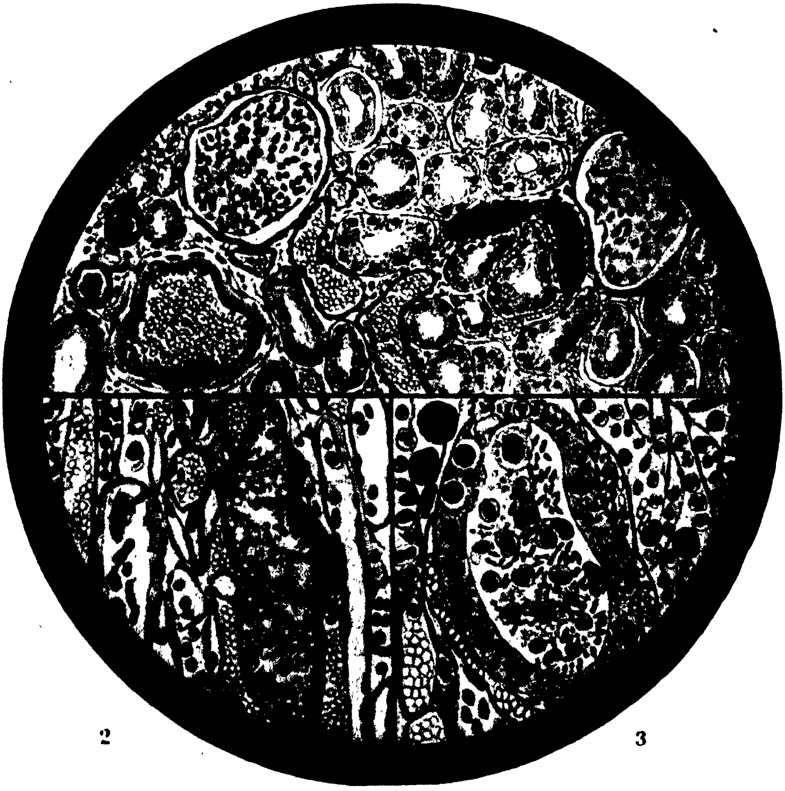


Fig. 53.—Sections of kidney in *Bact. coli* septicæmia.

1, Aggregation of organisms in intertubular capillaries; 2, large collection of organisms in a medullary vein; 3, passage of bacilli through tubular epithelium of duct of Bellini into lumen.

The original mandelic acid method has now been superseded by the use of more modern preparations, such as ammonium mandelate, mandelix and mandecol, in which ammonium chloride is combined with mandelic acid. These preparations are given as 1–2 drachm doses three times daily directly after meals until the urine has become sufficiently acid, the fluid intake being restricted to 40 oz. daily, and are very often successful in cases of pure *Bact. coli* pyelitis.

Sulphonamides have now come into use and threaten to supersede the mandelic acid preparations. They are especially useful in *Bact. coli* cystitis and trigonitis. The Editor employed sulphapyridine and sulphadiazine in doses up to 3 grm. daily for ten to fourteen days. This may be reinforced, if necessary, by after-treatment with mandelic acid preparations. Kenny, Johnston, and von Haebler (1937) recommended *p*-aminobenzene sulphonamide in the treatment of *Bact. coli* infections of the urinary tract. This is especially important in the *Bact. coli* pyelitis of children, and also in pregnant women. Comparatively small doses (1·5 grm. daily) effect a rapid disappearance of *Bact. coli* and pus cells and the remission of symptoms. The bactericidal power of the urine is roughly proportional to the sulphonamide content. The toxic manifestations of these drugs, which include sulphæmoglobinæmia or methæmoglobinæmia, are not common. In some patients they may produce headaches, or even drug fever and abdominal pain. Eggs and other sulphur-containing substances should be eliminated from the diet during the administration. It is necessary to estimate the leucocyte count at regular intervals, as leucopenia, or even agranulocytosis, may supervene.

It must be emphasized that, in employing these therapeutic measures, the condition of the kidneys and ureters should first be ascertained by means of excretion urography (uroselectan). Sometimes a calculus may be discovered in the renal pelvis or in the ureters, which may be the seat of the *Bact. coli* infection, necessitating surgical intervention.

Subsection E. DISEASES CAUSED BY VIRUSES

PRELIMINARY STATEMENT

VIRUS infections become increasingly important year by year as the number of human, animal and plant diseases attributed to the agency of viruses grows greater. The consensus of opinion now inclines to the view that bacteriophages must be included.

It is, however, recognized that not all viruses are alike. Certain plant viruses, such as those of tobacco mosaic and bushy stunt of tomatoes, and those affecting cucumbers, have been shown by Stanley in America and by workers in Great Britain, to consist of heavy proteins—almost certainly nucleo-proteins—with molecular weights of several millions. Certain of these viruses can be obtained in the form of true crystals. Although there is evidence that bacteriophage and some animal viruses may also be heavy proteins, no animal virus has yet been isolated in a crystalline form. The larger animal viruses, at any rate, are more complex, and a few of them, notably those producing psittacosis, inclusion conjunctivitis and lymphogranuloma inguinale, exhibit developmental phases.

Very frequently the adjectives "filterable" or "ultra-microscopic" are applied to viruses; both terms are unsatisfactory. Many of the smaller bacteria readily pass through filter candles, while the same is true of many spirochætes. Certain bacteria, such as those causing pleuro-pneumonia of cattle, or agalactia in sheep, also have filterable phases, while many true viruses only pass with difficulty through diatomaceous or porcelain filters. With ordinary microscopes, using direct illumination, the limit of resolution lies between 0.1 and 0.2 μ. Barnard, using ultra-violet light and special optical apparatus, was, however, able to photograph bodies of considerably smaller size. Many of the larger viruses, such as those of psittacosis, vaccinia, ectromelia, and herpes febrilis, have been successfully photographed, and stained, the dimensions obtained by these means agreeing very closely with those calculated from filtration experiments. A revolutionary method for visualizing virus particles is the magnetic electron microscope, or super-microscope, by which it is possible to obtain photographs of virus particles magnified by 20,000. The principle on which this instrument operates is that free electrons and beams of electrons can be deflected by an electromagnetic field. Such a field or magnetic lens is produced by a current-carrying coil. Probably the best working definition of viruses is that suggested by Gardner, who refers to them as "agents below, or on the borderline of microscopical visibility which cause disturbance of the function of living cells and are regenerated in the process."

Viruses may be precipitated and sedimented by centrifugalization. The majority of workers employed machines of high-speed type, but Craigie (1932) showed that they are not essential, since elementary bodies can be deposited at comparatively low speeds. Centrifuges fitted with angle type of head, and driven by directly coupled slow-running electric motor, are the best. This type was employed by Craigie. His success depends on the fact that flat glass tubes are used possessing an internal width of 4 to 5 mm. Consequently the elementary bodies have only to traverse a short distance before they strike the lateral wall of the tube, which is placed at an angle of 28° from the vertical. With such a centrifuge a speed of 3,500 r.p.m. for 60 minutes suffices for depositing the Paschen bodies of vaccinia.

History.—As early as 1728, twenty years before the birth of Jenner and long before bacteria were associated with disease, the term "virus" was applied to the casual agent of smallpox. Pasteur, in the course of his work on rabies, first suggested the possibility of ultra-microscopic organisms. It was only in 1892, however, that as a result of the work of Ivanovsky, the juice of tobacco-plants suffering from mosaic disease was found capable of infecting healthy plants after passing through bacteria-proof filters. In 1897 Loeffler and Frosch found by chance that foot-and-mouth disease could be produced by an " infective principle " which passed through porcelain filters. The infectivity of viruses for animals was thus demonstrated. Since that time more than 100 diseases due to filterable viruses have been discovered affecting man, mammals, birds amphibians, fish, insects, plants, and, if bacteriophage be included, bacteria.

Diseases caused by viruses.—In the list of infections produced by these agents must be placed mosaic diseases of plants, wilt and polyhedral diseases of insects, fowl-plague, fowl-pox, leukæmia, and filterable tumours of hens, infectious anæmia and Borna disease of horses, louping ill, foot-and-mouth disease, hog cholera, dog distemper, cat distemper, and—of special importance in the tropics—rinderpest of cattle, blue tongue of sheep, Nairobi sheep disease, and African horse sickness. The virus diseases of man which are of special tropical interest include smallpox and alastrim, rabies, yellow fever, dengue, Rift Valley fever, the D virus of Tunis, and other viruses from Uganda (Findlay), phlebotomus fever, psittacosis, trachoma, lymphogranuloma inguinale, and inclusion conjunctivitis. Many other virus infections are of universal distribution but may be responsible for severe epidemics in tropical countries. The list includes measles, influenza, varicella, rubella, mumps, herpes febrilis and probably herpes zoster, warts, molluscum contagiosum, anterior poliomyelitis, St. Louis encephalitis, Japanese type-B encephalitis, equine encephalo-myelitis, lymphocytic chorio-meningitis, and probably infective hepatitis, encephalitis lethargica and Australian X disease.

The action of viruses on cells.—The only certain method at present available of detecting the presence of viruses is by their pathogenic action on the cells of susceptible animals. It is possible that non-pathogenic free living viruses exist, and there is certainly evidence to show that many viruses may lead a more or less saphrophytic existence, only becoming pathogenic when inoculated into tissues other than those in which they normally dwell; examples are Virus III infection of rabbits, or salivary-gland disease of guinea-pigs. The virus of herpes febrilis may be found in the saliva of a high percentage of normal persons.

All viruses at present known are closely associated with living cells, and whether *in vivo* or *in vitro* require living cells for their multiplication. The action of viruses on cells is characterized either by stimulation or by depression of cell physiology; in certain instances a primary stimulation is followed by depression. Stimulation is characterized by active multiplication or hypertrophy of the cells, as in infective warts, fowl-pox, Shope's filterable rabbit fibroma, the filterable tumours of fowls, or fowl leukæmia. Depression is characterized by cell necrosis and is well exemplified by the action of yellow-fever or Rift-Valley-fever virus on the cells of the liver, or of poliomyelitis on the anterior horn cells of the cord. In certain cases the characteristic action of the virus may be manifested after a very short incubation period—mice inoculated with Rift-Valley-fever virus die in forty-eight hours with extensive liver necrosis—or viruses may lie dormant in the tissues for many weeks or months, as in rabies, Borna disease or lymphogranuloma inguinale virus when inoculated intracerebrally into mice. In scrapie, a disease of sheep, the incubation period is from sixteen months to two years.

In certain diseases the necrotic lesions are comparatively slight, but the resistance of the body to bacterial infection is greatly reduced. Sometimes the invading bacterium is specific, for instance, the virus of hog cholera is always associated with *Bact. suipestifer*, the virus of swine influenza with an influenza bacillus. At other times, as in human influenza, measles, or dog or cat distemper, the way is paved for the invasion of a variety of organisms.

The pathogenic action of certain viruses is restricted to the cells of one particular organ : other viruses are pathogenic for a variety of tissues. Many viruses display a special predilection for the cells of the central nervous system, while others, such as the viruses of yellow fever, Rift Valley fever, or horse sickness may, by intracerebral inoculation, be made to acquire such a predilection, at the same time losing many of their normal characteristics.

Inclusion bodies.—Histological examination of the lesions caused by many filterable viruses reveals the presence, either in the cytoplasm or in the nucleus of the cells, of peculiar cytological structures. These were at one period regarded as being themselves of a parasitic or possibly protozoal nature. The cytoplasmic inclusions vary greatly in type and in many cases their true nature is as yet unknown. The Negri body in rabies, for instance, may represent a stage in the complicated life-history of a parasite, or more possibly a reaction of certain cell structures to the virus. Certain cytoplasmic inclusions are undoubtedly made up of the virus particles, as in psittacosis, ectromelia, trachoma, lymphogranuloma inguinale, and smallpox ; or the virus particles may be surrounded by a cellular reaction, as in the Bollinger bodies of fowl-pox. The intranuclear inclusions, on the other hand, are more uniform in type. They occupy the nucleoplasm, may frequently be seen in the fresh unfixed cell, and tend to stain more or less intensely with acid dyes, such as eosin. Chemically they are not composed of chromatin, do not contain iron, and on micro-incineration yield only a fine ash. Closely similar structures may be induced in nuclei by the action of a number of chemicals. There is at present no direct evidence that they enclose the virus particles. Among the virus diseases which give rise to acidophilic intranuclear inclusions are yellow fever, Rift Valley fever, herpes febrilis, herpes zoster, varicella, Pacheco's parrot disease, encephalitis of silver foxes, pseudo-rabies, Virus III infection of rabbits, encephalo-myelitis of horses and " B " virus (*see* p. 348).

Cultivation.—One of the most important distinctions between viruses and visible bacteria lies in the fact that up to the present no true virus has been cultivated in the absence of living cells. The organisms of bovine pleuro-pneumonia, agalactia, and other pleuro-pneumonia-like organisms, which, formerly classed as viruses, can be grown on artificial media, are now generally regarded as true bacteria. Two methods are employed for the cultivation of viruses. The first method entails the use of an emulsion of minced embryo tissue suspended in Tyrode's solution and serum. The second consists in inoculating the virus on to the chorio-allantoic membrane of the developing chick embryo. On this membrane growth may entail either cell multiplication or cell necrosis.

Among the viruses which have been successfully grown by one or both of these methods are vaccinia, fowl-pox, Virus III infection, foot-and-mouth disease, yellow fever, Rift Valley fever, dengue, phlebotomus fever, louping ill, rabies, and pseudo-rabies.

Filtration.—Various types of filter are used in the study of viruses. The most important are those composed of diatomaceous earth (Berkefeld or Mandler filters), porcelain (Chamberland candles) and asbestos discs (Seitz filters). Passage through these filters depends, not only on the size of the virus particles, but on a number of physical factors such as the negative pressure employed, the rate of filtration, the nature and *p*H of the medium in which the virus is suspended, and the electric charges of the filter and virus particles.

Recently Elford has perfected the technique of making graduated collodion membranes, which have enabled measurements to be made of the approximate size of the virus particles. Results so far obtained give the following approximate dimensions :

Psittacosis	220 *m* μ	to	330 *m* μ[1]	(Levinthal,
Lymphogranuloma	125 *m* μ	„	175 *m* μ	(Miyagawa et al., 1935)
Vaccinia	125 *m* μ	„	150 *m* μ	(Elford and Andrews, 1932)
Rabies (fixed virus)	100 *m* μ		150 *m* μ	(Galloway and Elford, 1932)
Herpes simplex	100 *m* μ	„	150 *m* μ	(Elford, Perdrau and Smith, 1933)
Rift Valley fever	23 *m* μ	„	35 *m* μ	(Broom and Findlay, 1933)
St. Louis encephalitis	22 *m* μ	„	33 *m* μ	(Bauer, Fite and Webster, 1934)
Yellow fever	18 *m* μ	„	27 *m* μ	(Findlay and Broom, 1933)
Louping ill	15 *m* μ	„	20 *m* μ	(Elford and Galloway, 1934)
Foot-and-mouth disease	8 *m* μ	„	12 *m* μ	(Galloway and Elford, 1931)

[1] For value of *m* μ *see* p. 1020.

Physical properties.—The resistance of viruses to heat varies within very wide limits; to cold, on the other hand, many are extremely resistant and, especially when dried, may survive for many months. Many viruses, such as rabies, are extremely resistant to the action of glycerin ; others, like yellow fever, survive only a few days. Physiological saline or even Tyrode's solution is toxic to many viruses, but if serum is mixed with the fluid in the proportion of 1 in 10, it becomes much less toxic. Many viruses are very sensitive to the *p*H of the medium in which they are suspended, more especially when the reaction becomes acid. All the viruses so far examined carry a negative electric charge at *p*H's in the neighbourhood of neutrality. Many can be readily adsorbed on to finely dispersed substances, such as kaolin or animal charcoal, and, with the aid of suitable solutions, may be eluted from these substances, being thus obtained in a condition of relative purity.

The majority of viruses are easily inactivated by the photo-dynamic action of dyes such as methylene blue, or proflavine in dilutions of 1 in 50,000 to 1 in 100,000, when exposed to a pointolite. Certain viruses, such as that of dog distemper, when thus inactivated, retain to a certain degree their antigenic properties. Certain viruses, also, when killed by formalin, are still antigenic.

Immunity.—With but few exceptions, recovery from a virus infection is associated with a prolonged and sometimes life-long immunity. The few exceptions to this rule include herpes febrilis, the common cold, if it be really due to a virus, and dengue. Virus diseases thus differ as a class from bacterial infections, the majority of which do not leave an immunity of long standing. In many instances the prolonged immunity in virus infections is associated with the continued presence of virus in the tissues, but in others there is no evidence that it remains in a living condition.

Immunity is manifested by inability to re-infect with the same strain of virus as caused the original infection. It is important, however, to remember that in certain viruses, such as foot-and-mouth disease, influenza and probably dengue, a number of strains exist which are antigenically distinct and give no cross immunity. In the serum, immunity may be manifested by the presence of virucidal, complement-fixing and, in certain cases, agglutinating antibodies. In lymphogranuloma inguinale virus, a heated extract of the infected glands is capable of producing an allergic reaction when injected into the skin of an immune person, provided the infected material still contains virus particles.

Epidemiology.—The methods of spread of virus diseases are as numerous as those of bacterial infections. In certain instances direct contact with an infected person, as in warts and trachoma, or with infected fomites, is necessary, as in variola or varicella. Lymphogranuloma inguinale and venereal warts are spread by sexual contact. Droplet infection is responsible for the spread of measles, mumps, influenza, and probably anterior poliomyelitis, though it is claimed that certain epidemics of the last infection have been disseminated by infected milk. Insects may play a passive rôle, as in the transmission of fowl-pox, or may inoculate the virus by biting, as in yellow fever, dengue, equine encephalomyelitis, Japanese type-B encephalitis, and phlebotomus fever. Louping ill of sheep is transmitted by the tick *Ixodes ricinus* ; eastern encephalitis by *I. persulcatus*. Many plant viruses are transmitted by aphides or thrips.

Epidemiological considerations depend to a great extent on the immunity produced by a previous attack. When the number of non-immunes reaches a certain concentration, an epidemic may break out. Inapparent infections may at times serve to maintain an infection. Many laboratory workers, without experiencing actual infections, have in the course of their work become immune to diseases as diverse in character as poliomyelitis, louping ill, or Rift Valley fever.

Treatment.—In only two virus infections has any drug been found to have a specific action : in lymphogranuloma inguinale and trachoma, compounds of the sulphonamide group are of very considerable value. In other virus diseases treatment is necessarily symptomatic. When once a virus has gained entrance to the tissue-cells, even the specific immune serum is without effect, although, when administered within a short time after the inoculation of the virus, immune serum may decrease the severity of the attack or even entirely prevent it.

In many diseases immune bodies are formed in the tissues a short time after the beginning of the illness ; the patient may, however, subsequently die from the lesions which have been produced in the internal organs. Treatment must, therefore, be directed to maintaining the functions of the various organs, and to eliminating or destroying metabolic toxins.

Prophylaxis.—Prevention consists in destroying the virus and rendering the possible victims immune. In those virus diseases which are transmitted by insects, much may be done by destruction of the particular vector, though, in view of the wide areas over which a disease such as yellow fever is endemic, total elimination of the insect vector is well-nigh impossible.

In view of the definite immunity produced by most virus infections, however, the possibilities of prophylactic immunization are considerable. Immunity may be produced by the following :

(i) Immune serum,
(ii) Immune serum and living virus,
(iii) Virus attenuated by physical or chemical agents,
(iv) Virus modified biologically.

Immune serum is now largely used in measles prophylaxis. A temporary immunity only is obtained. Mixtures of immune serum and living active virus have been used in rinderpest and dog distemper. Virus attenuated or killed by physical or chemical means is also used in dog distemper and louping ill, while in rabies, fowl-pox, yellow fever, and African horse sickness, a biologically modified virus is employed, either alone, after further chemical or physical attenuation, or in association with immune serum.

It is probable that in the future prophylactic immunization will be extended to an increasing number of virus infections.

CHAPTER XVI

YELLOW FEVER

Synonyms. Typhus icteroides ; Fièvre jaune ; Fiebre a marilla (Spanish) ; Gelbfieber ; Amaryl (International nomenclature).

Definition.—An acute, specific febrile disease, due to a filterable virus, occurring epidemically, or endemically within a limited geographical area. Though subject to great variation and occurring sometimes in a mild form, its typical clinical manifestations may be said to be a sthenic initial stage, rapidly followed by an adynamic condition. Toxic jaundice and albuminuria commonly occur. One attack confers immunity for life. The virus is transmitted principally by the female mosquito, *Aëdes ægypti* (formerly *Stegomyia fasciata*) (*see* Fig. 362 and p. 974), which remains infective during its life.

History.—Though transmission of yellow fever through a mosquito was foreshadowed by Carlos Juan Finlay in 1881, a great advance was made in 1901 by the brilliant work of Reed, Lazear, Carroll, and Agramonte, who showed that the casual agent could pass through filter candles ; also, by their researches while living among yellow-fever patients in mosquito-protected wards and surrounded by the excreta and vomit of these patients, they proved that the transference of the disease under natural conditions takes place through the bite of the mosquito, *Aëdes ægypti.*

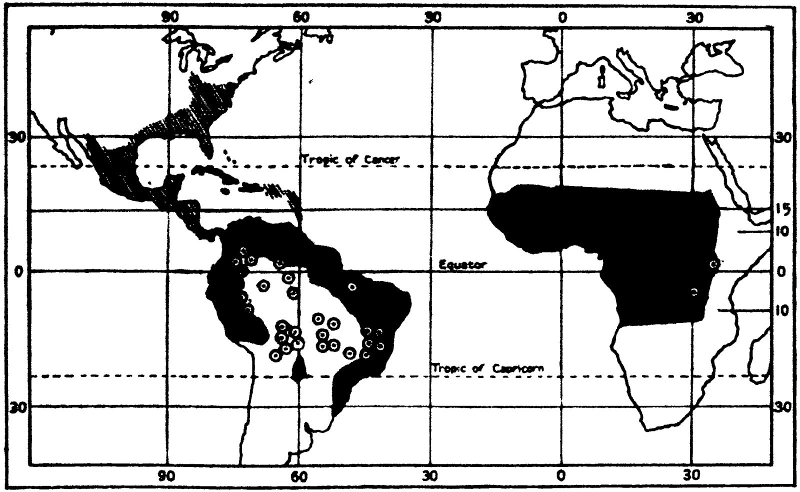
In 1928 Stokes, Bauer and Hudson showed that the rhesus monkey (*Macaca mulatta*) is susceptible to the disease, and that the causal agent is an ultramicroscopic virus. The virus can be transmitted to rhesus monkeys through many passages by blood inoculation and can be conveyed by the bite of infected aëdes from one animal to another almost indefinitely, though more recent researches have shown that in certain outbreaks and, under laboratory conditions, other mosquitoes also can transmit the virus.

In 1930 M. Theiler found that yellow fever may be transmitted to mice by intracerebral inoculation, producing meningo-encephalitis. After a number of passages in mice, the virus becomes fixed and, on re-inoculation into monkeys, does not give rise to ordinary yellow fever. The form of yellow-fever virus fixed for mice is now known as the " neurotropic ", in contradistinction to the " viscerotropic " strain.

The discovery of the neurotropic strain of yellow-fever virus has been followed by the development of an efficient prophylactic inoculation.

" Jungle " yellow fever has been recognized since 1932.

Geographical distribution.—This is considerably wider than was formerly supposed, though in former times the disease was common where it now no longer exists. For a great deal of our knowledge we are indebted to the labours of the International Health Division of the Rockefeller Foundation which, by means of the mouse-protection test (*see* p. 883), has shown that it can be determined whether yellow fever had been present in a district and, from the ages of those with positive protection, when the last epidemic occurred. At present yellow fever is mainly confined to South America, West and Central Africa (Map IV). In comparatively recent times it is known to have been widespread in the West Indies, Mexico and in the United States, as far north as Philadelphia (1798) and



▨ Area of epidemic yellow fever during the 19th century : now extinct.

■ Present distribution of clinical yellow fever.

■ Distribution of virus of yellow fever as shown by the protection test.*

⊙⊙⊙ Distribution of jungle yellow fever.

* Recent reports would indicate that this area extends at 15°N to the borders of the Red Sea.

MAP IV

Memphis (Mich.) (1878), and as far south as New Orleans and Galveston (1905). During the last century it was imported from time to time by ships to the Canary Isles, Spain, Portugal and to the small islands of Ascension and St. Helena in the South Atlantic, in all of which limited outbreaks took place. In 1865 a few cases occurred in Swansea, South Wales. The disease has never invaded Asia or Australia. It is by no means certain whether yellow fever originated in West Africa and was conveyed by ships to the West Indies and South America, or the reverse.

In South America yellow fever was endemic in Brazil, Bolivia, Colombia, Peru, Venezuela and Guatemala, and there is some evidence that it still exists in British and Dutch Guiana. In their campaign against yellow fever the Rockefeller Foundation concentrated on eradicating the "seed-beds of infection" on the South American continent in the belief that they were few. The clearing of Rio, Santos and Nichtheroy was followed by apparent disappearance of yellow fever from the whole of Southern Brazil. After a campaign in Guayaquil and another in Peru in 1920, no further cases were recorded on the Pacific Coast. Similar results were obtained in Colombia, Mexico and Central America.

In 1928–1929 yellow fever reappeared in Rio de Janiero. Soon locally infected cases occurred in the Brazilian States of São Paulo, Minas Geraes, Rio, Bahia, Sergipe, Pernambuco and Para. In 1932, by the introduction of the *viscerotome*, an instrument for obtaining liver tissue for examination, it was possible to prove the existence of "jungle yellow fever" (in the absence of *Aëdes ægypti*) in Espirito Santo. This is now regarded as the original and more permanent form of yellow fever. In West Africa yellow fever has long been known from Senegal to the Congo, while the long story of British endeavour in the development of West Africa, especially Sierra Leone and the Gold Coast, is one of struggle against yellow fever. (In 1826, out of the garrison of 535 soldiers, 115 were dead within two months, while of the first detachment of troops which occupied Cape Coast Castle in 1823 only one man was alive a year later. In 1878 an epidemic involved the whole of Senegal, affecting 1,474 Europeans.)

In the last epidemic in Accra in 1937 the native population was more severely affected than the European. Small outbreaks took place on the Congo at Matadi and Boma in 1927 and 1928, at Bathurst on the Gambia in 1935, and there were numerous other cases on the Gold Coast and in Nigeria in 1937 and 1938. The most extensive epidemic of yellow fever recorded in Africa broke out in the Nuba Mountains, Southern Sudan, in May, 1940, and there were 17,000 cases with a mortality-rate of 10 per cent. Previous to this, one single case of yellow fever had been recognized at Malakal in 1934. The epidemic subsided in November and was followed by a rise in the proportion of immunes in the population.

It has now been shown, as the result of immunity surveys, that yellow fever extends in a region from St. Louis on the coast of Senegal, just north of Cape Verde, eastward at latitude 15° N. along the southern borders of the Sahara through El Fasher to Dilling in the Southern Sudan. Thence the line bends southwards at Rashad in the Nuba Mountains, crossing the White Nile south of Jebelein, passes through Dar Fung, the area between the White and Blue Niles, up to and possibly beyond the

Sudan-Abyssinian border. A further extension eastward has recently been reported: to the N.W. boundary of Eritrea and the Red Sea coast, thence S. to the border of Somalia, at 36° meridian of longitude, south of Lake Rudolf. The eastern border runs through Western Uganda to the west of Lakes Victoria and Tanganyika, and thence diagonally at 10° S. parallel, across the Belgian Congo to the mouth of that river. In the west the line follows the Atlantic Coast from Senegal to Santo Antonio in the extreme north of Angola: a total area comprising approximately four million square miles. The islands in the Gulf of Guinea are included.

Finally, it is obvious that the geographical distribution of yellow fever does not correspond with that of *A. ægypti*, as the Orient, with its susceptible population and abundance of suitable mosquitoes, has so far remained free.

Epidemiology.—In former times it was generally considered that yellow fever was mainly confined to seaports and that it seldom spread far inland, but this is now known not to be the case. A study of epidemics shows that the virus of yellow fever can be readily transported from one place to another and that for its development in the mosquito it requires, usually, a mean atmospheric temperature of 75° F. (24–25° C.), and that endemic centres have never extended beyond 40° N. Lat. and 35° S. where the isotherm is not below 68° F. (20° C.). A high wet-bulb temperature favours yellow fever, so that it is most likely to arise and spread during the rainy season. It may, however, be found in mountainous regions up to 4,000 ft. In spreading inland it appears to follow lines of communication.

Conceptions on the epidemiology of yellow fever have had to be considerably revised since the discovery of the jungle form. Some authorities recognize three divisions—urban, rural and jungle—the last of which is thought to be the most primitive. Soper, on the other hand, favours the following classification:

(1) The urban and rural types are a domestic and purely human disease with a simple cycle of infection depending upon man and the insect vector, *Aëdes ægypti*, but they cannot continue to spread in the absence of *A. ægypti* mosquitoes in sufficient numbers.

(2) Jungle yellow fever, involving man and animals, in the absence of *Aëdes ægypti*, indicates that neither this insect nor man himself is an essential element in the insect vertebrate cycle of infection which maintains the reservoir of the virus in the jungle.

Jungle Yellow Fever.—It is now known that this form of yellow fever is conveyed by the bites of certain jungle mosquitoes (in Bolivia, Colombia and Brazil by *Aëdes leucocelaenus*, *Hæmagogus capricornii* and possibly also certain sabethine mosquitoes). There is now little doubt that jungle yellow fever exists also in Africa, in Uganda, North Kenya and possibly the Gold Coast, where isolated cases have been found in the bush, but the most important focus about which we have definite information was discovered by Mahaffy and his colleagues in 1941 in North Uganda, on the Semliki, west of Ruwenzori and on the eastern reaches of the Ituri river (Bwamba country). The northern half of this country is heavily forested, uninhabited except for pigmies. There the virus of yellow fever was isolated from humans as well as from wild-caught mosquitoes—*Aëdes simpsoni*—which appear to be the vector in this area.

The evolution of epidemics of yellow fever.—In experimental infection of humans, the shortest incubation period recorded is about two days. Under natural conditions it is from one to six and a half days. A period of at least fourteen days may elapse between the arrival of a yellow-fever-stricken patient in a hitherto uninfected district and the first case of the epidemic to which he may give rise. This would indicate that the period between the introduction of the virus into the body and the development of fever is usually some three to five days, yet a period of at least twelve days must elapse before that virus, removed from the human body, can be transmitted by mosquitoes to another. This is known as the *extrinsic period* and represents the time taken for the virus to multiply inside the mosquito, though experiments with these insects, when fed on monkeys, show that this may be reduced to eight or nine days at high temperatures, but at low temperature the mosquitoes *may never become infective.*

Conditions favouring endemicity.—For yellow fever to continue in an urban community three factors are necessary : (1) the virus, (2) the vector, and (3) susceptible human beings living under conditions in which both virus and man are easily accessible to the mosquito. A break in this chain suffices to eliminate the disease. In the urban, and more especially in the rural type, yellow fever cannot continue to exist in a community, unless *Aëdes ægypti* mosquitoes are present in sufficient numbers. But in a population which has become to a great extent immune to yellow fever it is obvious that a greater number of infected mosquitoes are necessary to maintain the virus. Thus, from time to time the disease has disappeared from towns in South America in which no sanitary work had been done to eliminate the mosquito ; the explanation being that there was a lack of susceptible persons to continue the existence of the virus in man.

Possibility of animal reservoirs of the virus.—The maintenance of the virus in endemic jungle yellow fever has been difficult to explain. It is possible that it might be carried on solely by the mosquito-man cycle through the combined presence of infected mosquitoes and frequent human cases. Thus, if cases were occurring continuously in man in any particular area, it should be possible to obtain the virus from the blood of these patients for, even if the vast majority had mild, or even sub-clinical symptoms, a few typical cases should be encountered from time to time. The second possibility is the existence of *an animal reservoir.* In 1914 Balfour drew attention to the great mortality amongst red howler monkeys (*Alouatta seniculus*) which preceded outbreaks of yellow fever in Trinidad and Venezuela. Amongst the natives the belief was strongly held that this presaged a human epidemic. Then Soper (1938), in an outbreak in the States of Minas Geraes and Rio de Janeiro, found increased mortality amongst these monkeys and, by protection tests, that they constituted an important factor in the spread of jungle yellow fever in Brazil. As the result of more recent work in South America it has been shown that inoculation of the virus into certain wild animals produces no appreciable illness, though it is still present in their blood for some days. Such animals are monkeys, opossums of all species, especially

Didelphis marsupialis, ant-eaters, sloths, armadillos, the agouti, paca, capybara and some mice. Their movements are unimpaired, and so the virus can spread over a wide area; transmission is probably affected by jungle mosquitoes.

In Central Africa there is some suggestive evidence. Pruner's hedgehog (*Atelerix albiventris*) has been found very susceptible to yellow fever, and the presence of immune bodies in the blood of a monkey, *Procolobus waldroni*, was verified by Findlay on the Gold Coast. He, moreover, showed that the sera of about 25 per cent. of the monkeys in Central Africa are protective.

It seems, therefore, that in rural and in jungle areas yellow fever may persist in the absence of susceptible humans. It is also a curious fact that normal cows' serum protects in certain instances. These findings seem to show that there are other methods of spread than by the mosquito-man cycle.

Immunity rate.—In areas outside the present known endemic zones of yellow fever, with few exceptions, no immunity against yellow fever exists. Thus, Sanger and his colleagues showed that of 876 human sera from Asia and Australia only 2 gave any protection, whilst amongst 481 sera from Italy, Portugal, Canada and Northern United States of America, even from some of the localities where yellow fever was formerly present, one only was protective. Sera were also tested from the West Indies, Barbadoes, Jamaica, St. Lucia, Trinidad, Cuba and Porto Rico. The sera of 821 people under twenty years of age were all negative, but above that age 8·42 per cent. gave positive protection tests. These results agree with the fact that yellow fever existed in all these regions until comparatively recent times. In Mexico, however, a higher percentage was obtained. From five to nine years, 0·9 per cent. were positive, from ten to fourteen years, 8·55 per cent., from fifteen to nineteen years, 28·81 per cent., but from twenty years and over, 42·72 per cent.

The results from the Sudan are of special interest as showing that outbreaks of yellow fever can to some extent be predicted. The examination of 43 sera from cases of jaundice resulted in some positives, *eight of which came from the Southern Sudan* and one from Wad Medani. In many of the villages in the Nuba Mountains 70 to 80 per cent. of positives were obtained, as also in the Fung area to the east of the White Nile, and this is where the outbreak took place in 1940.

Investigation of an area immediately after the subsidence of an epidemic, by means of the mouse protection test, reveals that the number of persons who give positive protection is much greater than the actual number of cases clinically diagnosed as yellow fever.

Ætiology.—A great many attempts have been made in the past to discover the germ of virus of yellow fever and many organisms have been described. The most ill-omened was undoubtedly the *Leptospira icteroides* of Noguchi, which eventually proved to be identical with *L. icterohæmorrhagiæ* of Weil's disease. The true nature of the virus was adumbrated by Reed, Carroll, and Agramonte who, in 1901, showed that it was filterable and ultramicroscopic. This was the first occasion in which it was proved that such a virus might be the cause of human disease

In 1929, Stokes, Bauer and Hudson clearly proved that the agent is ultramicroscopic and passes through Berkefeld filters V. and W. In 1933 Findlay and Broom, by employing Elford's system of ultra-filtration, were able to measure the particles of the virus (*see* p. 324). Sellards and Hindle showed that the yellow fever virus can maintain its vitality when dried *in vacuo* and frozen. When transported from Dakar to London the disease was reproduced in macaque monkeys by subcutaneous and intraperitoneal inoculation. When dried in the frozen state the virus retained its vitality as long as seven and a half years.

An important advance was made by Theiler (1930) who showed that white mice can be infected with yellow-fever virus by intracerebral inoculation and produce fatal meningo-encephalitis. Often, after a certain number of passages in mouse brains, it became established as the neurotropic virus, which no longer reproduces yellow fever of the usual type when monkeys are injected with the brain tissues of infected mice. Infection of rhesus monkeys can be produced by subcutaneous or intraperitoneal injection of infected blood or tissues or by smearing yellow fever blood on the unbroken skin, and the virus may be absorbed by the mucous membrane of the alimentary tract. In these animals the clinical and pathological picture of human yellow fever is reproduced and the virus is known as the viscerotropic strain. Rhesus monkeys artificially infected with this virus usually die from four to seven days after inoculation, before they have had time to develop immune bodies. The infective blood of monkeys may contain virus in dilutions as high as one in fifty million, and it may penetrate cell-free and protein-free fluids, such as the aqueous humour of the eye.

The virus is so virulent that infection of monkeys may occur from the bite of a single infected *Aëdes ægypti*. The species of monkey susceptible to the pantropic or viscerotropic strains are the rhesus monkey (*Macaca mulatta*), the crab-eating macaque (*M. irus*), the brown macaque (*M. fuscata*) and also, to a lesser degree, *M. sinica*. The Barbary ape from North Africa (*M. sylvana*) is also susceptible. Amongst New World monkeys, marmosets usually die, while some species of capuchin monkey recover after a febrile attack. Guinea-pigs are completely refractory, so that inoculation of these animals with blood from a suspected case serves, negatively, as a means of differentiation from *Leptospira icterohæmorrhagiæ*. European hedgehogs, more especially the Central African species, are very susceptible.

There is great variation amongst laboratory animals to intracerebral inoculation, and none react so constantly as do white mice. Under laboratory conditions African monkeys (*Cercopithecus*) are not always absolutely immune to the viscerotropic virus, but they do not react by fever and the virus circulates in their blood for a very short time.

The virus can enter the skin of man through conjunctiva or nasal mucosa under certain circumstances and cause fatal infections. This has occurred in autopsies on yellow fever cases in the early stage of the disease performed without rubber gloves. Laboratory workers have also become infected in examining monkeys after death. A number of isolated cases have occurred amongst laboratory attendants whilst undertaking blood examination of suspected cases, or whilst working with the virus. These infections, which numbered 35, were due to the pantropic and neurotropic strains (Berry and Kitchen) but, since the introduction of an efficient method of immunization, these laboratory infections have entirely ceased.

Cultivation of the virus.—The virus of yellow fever can be grown solely in the presence of living cells. Haagen and Theiler first succeeded in culturing the neurotropic strain in a medium of minced chicken embryo suspended in a mixture of normal monkey serum and Tyrode solution. Even after a hundred passages there was no appreciable loss of neurotropic activity. Subsequently Lloyd cultivated the pantropic virus (known as pantropic because it permeates all layers of the chicken embryo) which, after more than one hundred subcultures, had become attenuated and could, on this account, be used for protective vaccine. Later still, Elmendorf and Smith grew the pantropic virus on the chorio-allantoic membrane of the developing chick embryo which is the method now universally employed. Strain D-17 of the Rockefeller Institute is such an attenuated virus.

Terms employed for strains of yellow fever virus.—The terms *pantropic*, *viscerotropic*, and *neurotropic*, used in connection with the yellow fever virus, are sometimes rather loosely applied. The naturally-occurring yellow fever virus is pantropic and attacks all three embryonic layers of the chick embryo on culture but, when passaged through many series of mouse brains, it acquires affinity for nervous tissue and becomes the neurotropic strain. The viscerotropic, on the other hand, is one which has developed special affinity for organs other than the nervous system, particularly the liver, and it is produced by passage through the liver of rhesus monkeys. Sometimes, however, these strains are reversible and the viscerotropic will still cause a fatal encephalitis when introduced into the monkey brain, the liver being at the same time protected by a parenteral dose of immune serum. Some pantropic viruses from jungle yellow fever in South America have been found to be weak in both neurotropic and viscerotropic affinities, so that it is considered possible that both these could be enhanced by passage through mouse brain or monkey liver respectively.

The neurotropic strain of yellow fever virus.—Once the virus has become fixed for mouse brain it can be passaged indefinitely by intracerebral inoculation in these animals and subsequently, when injected intraperitoneally, it fails to kill. It causes meningo-encephalitis, not only in mice, but also to a lesser degree in guinea-pigs, agoutis, squirrels, peccaries, capybaras, coatis and field voles, as well as all species of monkey, and as a rule, viscerotropic lesions are not produced. Rats, rabbits, hamsters, pigeons, hens and canaries do not develop encephalitis. In hedgehogs, however, intra-cerebral inoculation may be followed by liver necrosis. Inoculation of neurotropic virus intrahepatically in rhesus monkeys sometimes causes reconversion into the viscerotropic strain. Unfortunately, the strains do not always maintain their type on subculture ; thus, reconversion of neurotropic virus to viscerotropic has occurred.

Physical properties of the virus.—The virus, both neurotropic and viscerotropic, passes readily through ordinary filters, Berkefield, Chamberland and Seitz. Findlay and Broom, by filtration through graded collodion membranes, have shown that its approximate size is between 18 and 27 mμ. Both the viscerotropic and neurotropic strains of virus are inactivated at a temperature of 60° to 65° C. When dried and frozen, the virus can retain its vitality for many months. It is inactivated by the photo-dynamic action of such dyes as methylene blue (1 in 100,000) and proflavine (1 in 50,000). The pantropic can withstand strong disinfectants, such as mercuric chloride, 1 in 7500, and phenol, 1 in 150, at 30° C. All strains carry a negative electrical charge at the pH of the tissues.

Protection tests as an index of endemicity.—The fact that, after an attack of yellow fever, immune bodies are present in the serum for the remainder of the patient's life, and that, when a mixture of immune serum and yellow fever virus is injected into susceptible animals, infection does not take place, suggested the practical application of "protection tests" for the diagnosis of recovered cases of yellow fever. If a mixture of the pantropic virus and the serum under examination is injected into a rhesus monkey, and if the serum contains immune bodies, the animal does not die. This was known as the "*monkey-protection test.*"

When, however, the neurotropic virus is employed, a mixture of the serum and infected mouse brain is injected intraperitoneally into mice which are simultaneously inoculated intracerebrally with starch. If the serum contains immune bodies encephalitis does not ensue. This is known as the "*mouse-protection test.*" Both tests possess a high degree of specificity, and results obtained by the two in the same areas of Africa and South America are in close agreement. The mouse protection test is now universally employed and has recently been simplified by modifications introduced by Whitman (1943). This is based on the greater susceptibility of immature white mice to extraneural injection of yellow fever virus. In mice between 18 to 21 days the degree of susceptibility is such that uniform death may be produced by injecting one tenth of the virus dosage required for adult mice without the need for *intracerebral* injection of starch. In these immature mice, when two parts of immune serum are added to one part of virus, the results of injecting 0·06 c.c. of the mixture are equivalent to injecting adult mice, which have received intracerebral starch, with 0·6 c.c. This obviously permits satisfactory tests to be made on much smaller serum samples than those required for standard tests.

The technique is as follows. Mice are injected with filtrates of 10 per cent. mouse brain virus. Three days later the brains are removed and emulsified in 15–20 per cent. suspension in saline and subsequently centrifuged at high speed for 40 minutes. The sera to be tested are measured into tubes in quantities of 0·4 c.c. each; 0·2 c.c. of virus is inserted into each tube of test sera and immune controls.

By this test it has been found that, both in Africa and South America, the areas which have been infected with yellow fever during the lifetime of the present generation are much more extensive than had been previously imagined. Despite the non-recognition of outbreaks of clinical yellow fever in native populations, it has been found in Northern Nigeria, for instance, that 80·4 per cent. of sera are positive. Somewhat similar results have been obtained from French West Africa and the Southern Sudan. There is some evidence that the immune bodies may pass from mother to child by the milk. Monkeys born of immune mothers possess immune bodies in their serum at birth.

Transmission of the virus through the mosquito.—The virus multiplies in the insect vector during a variable extrinsic period. During this period the mosquito is not capable of transmitting the virus by its bite. In *Aëdes ægypti* it ranges from 4 days at 98·6° F. (37° C.) and 12 days at 78·8° F. (26° C.) to 18 days at 69·8° F. (21° C.). Under natural conditions the percentage of mosquitoes becoming infected is small. Possibly this may be explained by the small quantity of blood (0·01 c.c.) imbibed by *Aëdes ægypti*. There is no proof that the virus is hereditarily transmitted through the mosquito.

Observations on the habits of *A. ægypti* indicate that the female does not lay eggs until she has fed on blood, and that these are deposited three days after feeding. At this stage she is especially susceptible to infection with the yellow fever virus (*see also* p. 974). The course of development of the virus in the mosquito has not been traced. The type of development appears to be simple for, if infective mosquitoes are ground up and fed in syrup to normal *A. ægypti*, they too become infective after the usual extrinsic period. It has been shown that the virus undergoes multiplication in the mosquito and that it is present in its alimentary canal for at least ten days after an infective meal. Subsequently, it becomes centred in the salivary glands.

Species of mosquito, other than A. ægypti, capable of transmitting the virus.—In South America jungle yellow fever occurs in the absence of *A. ægypti*. Other species have been found infected: *Aëdes leucocelænus*, *Hæmagogus capricornii* and some sabethinæ. In Central Africa *Aëdes simpsoni* has been proved to be the vector of jungle yellow fever. The jungle species of mosquito vectors are usually inhabitants of the tree tops and rarely descend to ground level. In the Southern Sudan *Tæniorhynchus africanus* has been suggested as the vector of epidemic yellow fever. The following species of mosquito have been found capable of transmitting the yellow fever virus under laboratory conditions, but probably not all do so naturally.

European mosquitoes: *Culex fatigans*, *Aëdes geniculatus*.

African mosquitoes: *Aëdes vittatus*, *A. luteocephalus*, *A. africanus*, *A. furcifer*, *A. simpsoni*, *A. stokesi*, *A. taylori*, *A. metallicus*, *Tæniorhynchus africanus*, *Culex thalassius*, *Eretmopodites chrysogaster*.

Asiatic mosquitoes: *Aëdes albopictus*.

South American mosquitoes: *Aëdes fluviatilis*, *A. scapularis*, *A. leucocelænus*, *Hæmagogus janthomys*, *H. capricornii*.

North American mosquitoes: *Aëdes triseriatus*.

In a number of other species the virus remains active for a considerable period, but is not transmitted by biting.

General observations.—The observations which have been made upon the ætiology of yellow fever appear to explain some generally accepted facts.

(1) The impunity with which a yellow fever patient can be visited by a non-immune person, if outside the endemic area. The mosquitoes in the vicinity are not infective.

(2) The danger of visiting the endemic area when mosquitoes are both active and infective. *A. ægypti* usually feeds in the late afternoon, though

this does not hold good in the case of jungle yellow fever, where the forest-living mosquitoes in South America bite during the day time.

(3) The discrepancy between the incubation period, three to five days, of the disease, and the incubation period, fourteen days and over, of an epidemic. The evolution of the virus in the mosquitoes infected by the original patient demands the space of time indicated by the difference between these periods.

(4) The clinging of yellow fever infection to ships, buildings and localities. This is due to the persistence of the virus in infected mosquitoes (*Aëdes ægypti*) which are now known to be capable of surviving for five months, possibly longer, after feeding on human blood.

(5) The higher atmospheric temperature required for the epidemic extension of yellow fever. Such temperature favours the activities of the mosquito and is necessary for the evolution of the virus in the insect.

Biochemical changes produced by the virus.—All the biochemical changes which occur in yellow fever can be interpreted as an interference with the liver and kidneys. Thus, there is loss of glycogen from the liver and a considerable reduction in the blood-sugar. Findlay and Hindle showed also that, as in other toxic affections of the liver, there is, in rhesus monkeys and in humans, an increase in the blood of guanidine-like substances. The repeated administration of calcium lactate in large doses reduces this excess of guanidine and may play a part in preventing gastric hæmorrhage.

Pathology.—The pathological appearances vary very greatly with the clinical course of the disease. In typical cases the olive-yellow colour of the skin is most marked in the dependent parts of the cadaver, especially in parts subjected to pressure. Rigor mortis is pronounced. Petechiæ are common in the skin and serous membranes ; more considerable extravasations of blood may be found in the muscles. The brain and meninges are hyperæmic and may be studded with minute effusions ; like the other tissues of the body, they may be stained a lighter or deeper yellow. The cartilages are intensely yellow.

The blood in the vessels of the general circulation is not firmly coagulated. An important fact, as explaining the liability to passive hæmorrhages, is the existence of a generalized fatty degeneration of the capillaries and smaller blood-vessels. The stomach usually contains black or fluid blood. The folds of the gastric mucous membrane are swollen and there are arborescent patches of ecchymosis. The small intestine contains a dark material similar to that in the stomach. Only after microscopic examination of the organs, especially the liver, can a pathological diagnosis of yellow fever be made.

The virus of yellow fever, like certain other viruses, has a particularly destructive action on the liver cells, and by microscopic examination of liver sections alone it is usually possible to arrive at a diagnosis. In the early stages the liver is red from extravasation of blood, but if death has occurred later, the organ is usually somewhat friable and may present a yellowish colour which has been compared with that of box-wood. The microscopic pathology of the liver is well-defined and differs from that produced by any other infectious disease. The most marked changes are found in the mid-zonal region of the liver lobules, to a lesser extent at the periphery. The liver cells are often separated one from another and tend to assume a rounded shape; fatty degeneration may be very intense (Fig. 54). The typical lesion is a coagulative necrosis with a marked edge, surrounded by a narrow clear halo. Frequently the cytoplasm in whole or in part undergoes a hyaline degeneration—hyaline coagulation necrosis—together with hyaline bodies, first described by Councilman, while the cytoplasm of all the liver cells stains more intensely with acid stains such as eosin. The necrosis of the liver is not exactly a *midzonal necrosis*, as is often stated, but is a salt and pepper necrosis occurring throughout the lobule. The nuclei of the liver cells exhibit margination of the chromatin round the nuclear membrane, while in some cells the nucleoplasm is occupied by acidophilic intranuclear masses (Fig. 55). Hyperplasia of the Kupffer cells is usually noted. Usually only a small number of cells is affected, but with certain strains 70–80 per cent. exhibit inclusions. In the rhesus monkey, a high percentage of cells always shows intranuclear inclusions. These were first described by Torres and specially studied by Cowdry and Kitchen; they are similar in type to, though not identical with, those found in many other virus diseases. Within the liver lobules there is hyperplasia of the endothelial cells of the sinuses and an infiltration with large mononuclear cells and a few polymorphonuclear leucocytes. In the rhesus monkey the infiltrating cells are predominantly polymorphonuclear, while 80-90 per cent. of the parenchymatous cells contain acidophilic intranuclear inclusions. Councilman lesions, on the other hand,

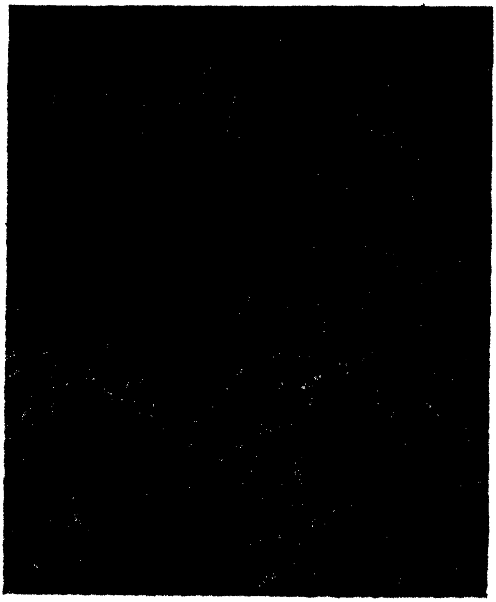


Fig. 54.—Yellow fever: section of liver (low power) showing fatty and hyaline degeneration and Councilman lesions. (*Dr. G. M. Findlay.*)

are comparatively rare, while fatty degeneration is also less marked than in man.

In the spleen there are no characteristic changes, but the endothelial cells of the splenic sinuses may show hyperplasia, while the Malpighian corpuscles are somewhat atrophied. Definite changes, however, are found in the kidneys. The reaction is a *nephrosis*, not a nephritis. Hæmorrhagic foci under the capsule and in the cortex are common. The renal epithelium shows cloudy swelling, passing on to fatty degeneration which affects the tubules more than the glomeruli. The tubules, here and there, are filled with casts, either of an albuminoid material or of débris of desquamated epithelium, corresponding with the casts in the albuminous urine. Granular and hyaline casts are found throughout the tubules of both cortex and medulla. Hoffman regarded lime-casts in the convoluted tubules as distinctive of yellow fever. Degenerative changes occur in the heart muscle, including the bundle of His. Although the virus is highly neurotropic, no extensive lesions of the central nervous system are found.

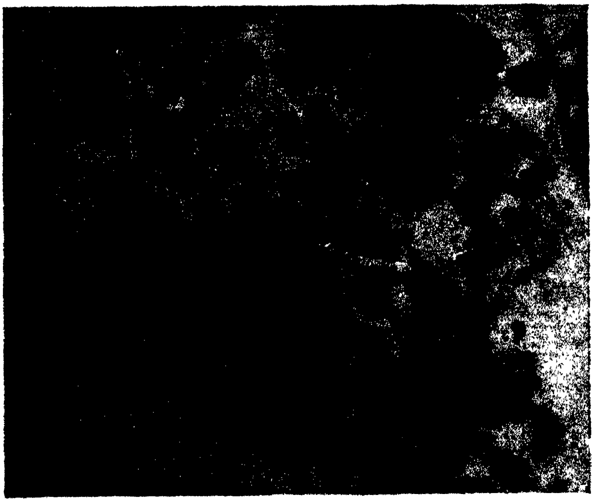


Fig. 55.—Yellow fever: section of liver × 2,000 showing acidophilic intranuclear inclusions (Torres bodies) and Councilman bodies. (*Dr. G. M. Firdlay.*)

Symptoms.—There is the same variety in the initial symptoms of yellow fever as in other specific fevers. In both urban and jungle yellow fever many mild and clinically unrecognizable cases occur. In the first stage they may range from an almost imperceptible febrile reaction to severe prostration.

Roughly speaking, and provided there are no complications, an attack of yellow fever is divisible into three stages—(1) the initial fever; (2) the "period of calm"; and (3), in severe cases, the period of reaction.

The initial fever is usually sudden in onset, and lasts from three to four days. The maximum temperature is generally attained within the first twenty-four hours, or by the second day, and, in a case of medium severity may rise to about 103° or 104° F. During the three or four succeeding days the mercury slowly sinks to 98° or 99° F., the daily fluctuations being seldom more than a half to one degree. It occasionally happens that high temperature is maintained for more than three days, and also that the maximum is not attained until the eighth, but, as a rule, it is reached within two days of the onset (Chart 19).

With or soon after the initial chill or rigor, severe headache sets in and is generally a prominent feature. For the most part the pain is concentrated about the forehead, in the circumorbital region and in the eyeballs. In many cases it is associated with intolerance of light.

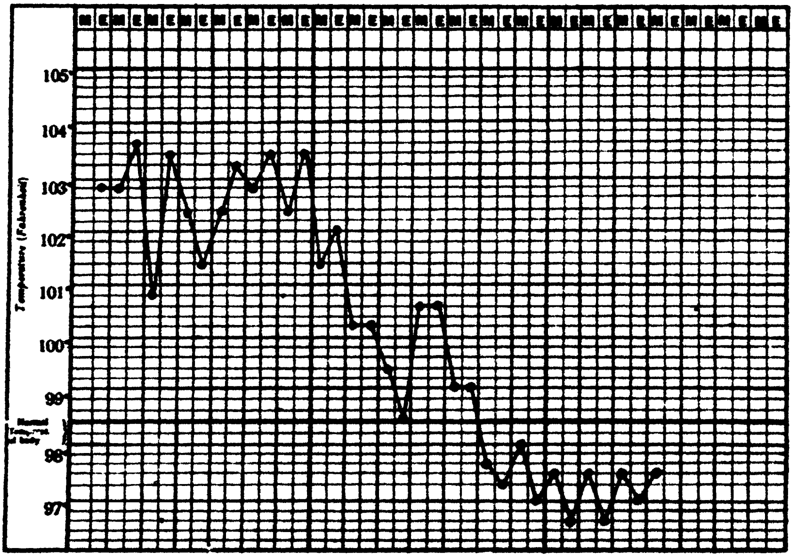


Chart 19.—Laboratory infection of yellow fever. Recovery.

Loin pain is another very distressing symptom; it may amount to positive agony; the backache may be as bad as in a severe case of smallpox. The legs, too, ache excessively—particularly the calves, knees, and ankles; they feel as if broken. Epigastric pain is generally prominent.

The face is flushed and swollen; the eyes are shining, injected, and ferrety; the skin is dry.

What with pains and febrile distress the patient passes into a very miserable condition. He is restless and continually tossing about.

At first the pulse ranges from 100 to 120, and is full and strong; but as the disease progresses, the pulse loses its sthenic character, gradually falling in force and frequency until, at the "period of calm," it becomes remarkably slow and compressible, beating perhaps only 30 or 40 times per minute. This fact may be of particular value in diagnosis, and is known as *Faget's sign*—that is, a falling pulse-rate with a constant temperature, or a constant pulse-rate with a rising temperature. It is in fact a sign which emphasizes the lack of correlation of temperature and pulse, so that by the second day, notwithstanding the high temperature, the pulse-rate becomes less, and by the third or fourth day it has probably decreased 20–40 beats from its initial rate.

At the outset the tongue is not very dirty, but it soon acquires a white coating on the dorsum, the edges remaining clean. It is not so swollen and flabby as in malarial fever; on the contrary, it is rather small and pointed throughout the disease. This is regarded as an important diagnostic mark; taken along with the progressive diminution in the strength and frequency of the pulse and the peculiar behaviour of the temperature, it is nearly conclusive of yellow fever. Later, the tongue dries and, at the same time, thirst becomes intolerable. The palate is congested and swollen; the gums may also swell and bleed.

The congested appearance of the face at the onset of the disease tends to subside; so that by the time the asthenic stage is reached the features may have become small, the eyes sunken, and the eyelids discoloured by ecchymoses.

In some cases the skin is hot and dry throughout; in others it may be bedewed with perspiration from time to time; or the sweating may be constant, especially if collapse sets in.

By the third day the scleræ assume a yellowish tinge, and very often the skin acquires that yellow colour from which the disease derives its name. In severe cases bluish spots may be observed and are due to subcutaneous hæmorrhagic effusions. It must not be understood, however, that every case presents this colour of skin; in some it is entirely absent, but if carefully looked for there is always some yellowness of the scleræ. The yellow tinging of the skin generally shows about the end of the first stage, deepening in intensity as the case advances, and remaining apparent for a considerable time after convalescence has become established. It ranges in depth from a light saffron to a deep mahogany brown. In fatal cases it is always present—not necessarily during life, but invariably after death. The skin in bad cases is said to emit a peculiar odour like gun-washings, or, as Jackson puts it, like the smell of a fish-market.

Petechial, erythematous, papular, and other eruptions may show themselves in different cases; but in yellow fever there is no characteristic eruption, unless it be an erythematous congestion of scrotum or vulva, which occurs in a proportion of cases and is described as diagnostic.

An important feature, from the diagnostic as well as from the prognostic point of view, is the appearance, in some cases almost from the outset, of albumin in the urine, together with a tendency to suppression. At first urine is abundant, but chlorides diminish rapidly, and suppression, according to Pichat, appears towards the end of the second day. In mild cases these changes may be little marked; but in severe cases, particularly during the stage of depression, the urine may fall to a few ounces, and be loaded with albumin to the extent of one-half or even two-thirds (usually about 2 grm. of albumin per litre). The more pronounced these symptoms, the graver the prognosis. The amount of albumin increases as the temperature falls. Urea (even during the incubation period) and uric acid are very much diminished, the former in severe cases falling to 1.5 grm. to the litre. The urine is almost invariably acid, depositing granular casts, and sometimes giving spectroscopic evidence of hæmoglobin. Bile-pigments and bile-stained tube-casts show themselves towards the end of the disease, usually about the fifth day, and their appearance is regarded as a favourable omen. Peptonuria indicates a serious prognosis. The blood urea is usually high during the terminal stages.

Insomnia is usual, but if it occurs before the third day prognosis is said to be grave. Delirium may occur, but is not invariable. Usually, after the initial stage of restlessness and acute suffering, the patient becomes torpid, and perhaps taciturn. In bad cases coma and subsultus may gradually supervene, the temperature rising as death approaches, and even after. A well-marked *tache* is present on the forehead, as well as on other parts of the body.

At the outset the bowels are confined. In the second stage, diarrhœa, perhaps of black material resembling the vomit, may supervene ; or there may be actual hæmorrhage of bright-red blood from the bowel.

Nausea and vomiting are more common than in other fevers. The well-known *black vomit*—always a grave symptom, but fortunately not by any means an invariable one—forms one of the most striking features of this disease. In the earlier stages of the fever, vomiting of bilious matter is common. This may subside or, after a time, give place to " coffee-grounds " which seem to gush up without straining or effort on the patient's part, and which gradually deepen in colour until they become uniformly black. On microscopical examination the vomited material is found to consist of broken-down blood-corpuscles and altered hæmoglobin suspended in a yellowish mucoid fluid. This material is, doubtless, in the main derived from blood transuded through the walls of the capillaries of the mucous membrane of the stomach. It is intensely acid. Though the black vomit may not always be seen in fatal cases during life, the material is invariably found in the stomach *post mortem*.

Sometimes pure blood is thrown up from the stomach ; similar passive hæmorrhages may take place from almost any part of the body—from eyes, ears, nose, mouth, bladder, uterus and so on. " Everything is congested at the outset, everything bleeds at the end," is a well-known adage.

Death may occur during the early acute stage, being preceded by a rapid rise of temperature. The majority of deaths occur on the fifth and sixth days ; the end seldom comes before the third or after the eleventh day, and, at this stage, is generally preceded by a rapid fall of temperature.

In mild cases the " period of calm," which sets in after the subsidence of the initial fever, may last for several days, before convalescence. The most constant symptoms are headache, pain in the back and extremities, photophobia, anorexia, prostration, congestion of the eyes, with a typical tongue, pointed and coated, but with red edges and tip. In such cases, recovery, once begun, is usually rapid ; in a week from the beginning of the disease the patient may be about again. In severe cases, however, the period of calm is followed by a third stage, the stage of reaction, in which the temperature again rises, though not to so high a point as in the initial fever, and a sort of remitting fever of an adynamic type keeps on for several days or weeks. This secondary fever is more prolonged if there is any complication, such as abscess, boils, parotitis, buboes, or secondary hepatitis. The icterus is now very pronounced ; black vomit may recur, or appear for the first time ; perhaps a profuse diarrhœa ends in collapse ; or the urine may be suppressed, stupor, coma, and other nervous symptoms ensuing, and very often ending in death. In other instances the secondary fever terminates in a crisis of sweating and prolonged convalescence.

Even in Europeans, as illustrated by certain of the infections contracted in the laboratory, yellow fever may be comparatively mild and may resemble an attack of influenza.

Relapses are rare, and when they do occur are dangerous. The immunity produced by one attack of yellow fever is usually permanent, as permanent as that produced by smallpox or measles.

As a rule there is no anæmia, but there is a slight leucocytosis early in the disease, soon followed by a leucopenia, which reaches its lowest point about the fifth or sixth day (Berry and Kitchen) ; the polymorphonuclear cells predominate, and there is an increase of mononuclear cells during convalescence. In human infections the virus has been shown to exist in the blood 107 hours after the onset of fever, while antibody has been detected after 83 hours, thus confirming what had already been suspected on epidemiological grounds of the simultaneous presence of virus and antibody in human blood in yellow fever. In icteric cases the Van den Bergh reaction is biphasic.

Experimental yellow fever infection in monkeys leads to a febrile reaction which is not high during the early days of the illness, but subsequently there is a sudden rise of temperature followed by a rapid fall and the animal dies in coma. In some there is an alternating rise and fall and in others a rapid crisis and death. Death may take place as early as the fourth or as late as the fifteenth day. In endemic areas many native children develop unrecognized infections.

Diagnosis and differential diagnosis.—Routine urine examination must be carried out in all febrile cases and all with more albuminuria than justified by the degree of fever should be considered suspect. Other points to be considered are the severity of initial symptoms, the relation of pulse and temperature to different stages of the disease, the intensity of the albuminuria, the degree and colour of the jaundice, the time of the appearance and the occurrence of hæmorrhages. Severe yellow fever may be confused with *remittent subtertian malaria*, Weil's disease, *infective hepatitis*, and *blackwater fever*. The difficulties of clinical diagnosis are often great, especially early in an epidemic. When several deaths, preceded by fever and black vomit, have occurred within a limited area and in quick succession, a suspicion of yellow fever becomes a certainty, though sometimes this has been observed in Weil's disease. There is no clinical feature, so far as is known, which would distinguish a mild attack of yellow fever from an ordinary febricula, nor any pathognomonic clinical sign that would absolutely distinguish a malarial remittent from yellow fever and from Weil's disease. *Dengue* is probably one of the most difficult diseases to differentiate from mild yellow fever. The facies, orbital pains, and backache are similar to those of dengue, but the appearance of the characteristic eruption of the latter disease on the fourth day should settle the diagnosis in any doubtful isolated case. Probabilities must be weighed in diagnosis when it is based on clinical grounds alone. The only reliable guides, as between malarial and yellow fever, are the discovery of the malaria parasite, the characteristic pigment and leucocytic variation in the one, and the determination of their absence in the other, but in an area where malaria is endemic, the finding of parasites does not rule out concomitant yellow fever. *Post mortem*, the presence of pigment in the viscera in malaria, and of extensive necrosis of the liver-cells in yellow fever is diagnostic. Biopsy of liver tissue by a special trocar will probably be of value in doubtful cases. Occasionally the two diseases may co-exist. The presence of albuminuria is of value in early and abortive cases, especially in Europeans, but albuminuria is more easily provoked in West Africans from any cause.

In addition to the diseases mentioned, there is great difficulty clinically in diagnosing yellow fever from Rift Valley fever, or, in its milder manifestations, from some forms of influenza, especially of a virulent strain. Occasionally relapsing fever may assume a malignant form with intense icterus and resemble yellow fever in its clinical manifestations, but it may be distinguished by leucocytosis, splenomegaly and spirochætes in the blood. Smallpox, in the first three days, before the rash, may be very similar to yellow fever.

It must also be remembered that in adults infective hepatitis may occur in severe form, while unexplained outbreaks of fever and jaundice, not due to the yellow-fever virus, have been described (*see* p. 348). These diseases have been differentiated by failure to infect rhesus monkeys during the acute stage, and by the absence of immune bodies to yellow fever in the blood. In West African natives, particularly, jaundice and albuminuria are common accompaniments of lobar pneumonia and exceptionally of relapsing fever.

Laboratory diagnosis.—With modern advances in our knowledge of the ætiology of yellow fever, an increasing confidence is being felt in its diagnosis. Within the first three days of illness yellow fever is readily transmitted by inoculation of the blood to rhesus monkeys which die after an interval of four to five days. Blood which has been kept at the temperature of the ice-chest may retain its infectivity for several days. Direct inoculation of infected blood into the brains of mice gives rise to an encephalitis in from seven to fifteen days. For the diagnosis of recovered cases there is the monkey- or, preferably, the mouse-protection tests.

In fatal cases yellow fever may be diagnosed *post mortem* from a histological examination of the liver, the essential features being the fatty degeneration, mid-zonal necrosis, infiltration with mononuclear cells, and the presence of Councilman lesions (hyaline bodies) and acidophilic intranuclear inclusions. The employment by the International Health Division of the Rockefeller Foundation of the " viscerotome " enables portions of liver to be removed from a cadaver without a general post-mortem examination. An examination of the livers of all those who have died from acute disease has, in South America, enabled many unsuspected cases of yellow fever to be accurately diagnosed, and there is now a well-organized viscerotome service.

In any outbreak of febrile illness with jaundice in an area where the mosquito fauna would permit yellow fever to spread, it is important that blood from recovered patients be examined for yellow fever protective bodies, and liver tissue of cadavers for the appearances typical of yellow fever. By these means, in countries hitherto not invaded by yellow fever, early information may be gained and steps can be taken to control the disease.

Complement fixation.—Attempts have been made to discover some simple test for yellow fever which would obviate the more elaborate protective tests in experimental animals. Davis, Frobisher and Hudson have made numerous experiments using, as an antigen, either plasma, serum or liver obtained from monkeys on the first or second day of fever. The concentration of complement-fixing bodies was found to reach its maximum in monkeys after thirty to forty days, and they remained in the circulation for a few months to more than one year. Only inconstant results were obtained with human serum.

Prognosis and mortality.—Prolonged initial rigors, algidity, convulsions, suppression of urine, coma and hæmorrhages are all unfavourable symptoms. The prognosis is good if the temperature during the initial fever does not exceed 103° to 105° F. It is better for women (although, if pregnant, abortion is almost invariable) and children than for men ; better for old residents than for newcomers ; worst of all for the intemperate. According to a table given by Sternberg of 269 carefully observed cases, there were no deaths in 44 in which the temperature did not rise over 103° F. ; in 22 cases in which the thermometer rose to over 106° F. there were no recoveries. The mean mortality in the whole 269 cases was 27·7 per cent. In some epidemics it has risen as high as 50 or even 80 per cent. of those attacked, but between 25 and 30 per cent. may be taken as a fairly representative mortality among the unimmunized. Among the permanent inhabitants of the endemic districts the case-mortality is very much lower—7 to 10 per cent. In the recent outbreak in the Sudan it was about that figure. During epidemics, abortive and ambulatory cases occur ; in these, icterus and other characteristic symptoms are often absent. Such cases may be hard to diagnose from febricula or mild malarial attacks, and the mortality is nil. Some epidemics are particularly mild : in others, the majority of the patients die. In the same epidemic the cases may vary in severity from time to time. In children the mortality is insignificant.

TREATMENT

Formerly a much more active treatment than that in vogue at the present day was the fashion for yellow fever. It is now recognized that, as with most specific fevers, the treatment is more a matter of nursing than of drugs. Once in bed, the patient should not be allowed to get up. As in other virus diseases the injection of immune serum is valueless once the infection has begun ; given during the incubation period, however, it may prevent, or at any rate decrease, the severity of the disease. Since the virus is efficiently neutralized by the formation of immune serum by the fourth or fifth day after the onset of fever, it follows that death is caused by the destructive effect of metabolic toxins on the liver, heart and kidneys.

Experience has shown that a smart purgative at the very onset of the disease is beneficial. With many, castor oil is the favourite drug, but to be of service it has to be given in very large doses—2 oz. or more. Others use calomel, or calomel combined with quinine. Others, again, prefer a saline.

Hot mustard plasters, frequently repeated during the first twenty-four hours, are much in favour. They are said to relieve the cerebral congestion and the intense headache. Hot baths, with subsequent blanketing and sinapisms to the epigastrium, are said to have a similarly favourable influence on the congestion of the stomach, which is, undoubtedly, another constant feature. For high fever, antipyretic drugs, cold baths, iced injections, cold sponging and the like may be carefully employed. In view of the asthenic nature of the disease, the less depressing measures should be preferred.

Vomiting may be treated with sinapisms and ice pills, or with small doses of cocaine. Luminal is indicated to induce sleep in restless cases, and codeine sulphate to relieve headache and backache. For black vomit, frequent doses of perchloride of iron, ergotine injections and acetate of lead have been recommended. Calcium lactate, in large and repeated doses by mouth, is probably of value in counteracting the excess of guanidine in the blood. The administration of glucose in the treatment of the hepatic conditions represents a distinct advance, and good results from this line of therapy have been reported. Glucose should be given in drachm doses, whenever feasible or, when nausea is present, in 5 per cent. solution intravenously (10 oz.), while injections of 5 units of insulin improve its assimilation. For restlessness, phenacetin or antipyrin is used. When the skin is dry, the urine scanty, and the loins ache excessively, Sternberg recommended pilocarpine.

After the fourth or fifth day the flagging circulation demands stimulants of some sort. Iced champagne, hock, or teaspoonful doses of brandy, given every half-hour, may tide the patient over the period of collapse. Great care, however, should be exercised in the use of these things; if they seem to increase the vomiting and the irritability of the stomach they must be stopped at once.

Free ingestion of water tends to obviate failure of renal function, which is the usual form of death.

The feeding is important. So long as there is fever the patient has no appetite; during this time—that is, for the first two or three days—he is better without food. When the fever subsides appetite may return, and a craving for nourishment becomes more or less urgent; the greatest care, however, must be exercised about gratifying this untimely appetite. Only the blandest foods, and those only in very small quantities, should be allowed—such as spoonsful of albumin water, barley water, iced milk or chicken tea. Gradually the quantities may be increased; but, even when convalescence is established, solid food must be taken very sparingly, and must be of the simplest and most digestible kind. Indiscretion in eating is a fruitful cause of relapse in yellow fever; and in this disease relapse is exceedingly dangerous. Nutrition may be aided by nutrient enemata. Any slight exertion which may cause a rise in blood-pressure may be fatal. It is possible, too, that stimulation of the circulation incident to the taking of food explains the dangers of altering food during the early stages.

Sternberg advised an alkaline mixture containing gr. 150 of sodium bicarbonate in a quart of water, of which 1½ oz. is given every hour, as a method of counteracting the hyperacidity of the gastric and intestinal contents.

Any suspected case of yellow fever should be nursed under a mosquito-net day and night, and preferably in a mosquito-proof room.

Prophylaxis.—A period of six days' quarantine is now accepted by the international sanitary convention as necessary after exposure to infection. It is the duty of sanitary authorities in tropical countries to free the areas over which they have charge from *Aëdes ægypti* mosquitoes as far as possible. Although complete destruction is not to be expected, relative extermination of mosquitoes is worth attempting, and certainly can be attained by the vigorous use of the now well-known measures. In Havana, by such means, in a very few months the number of mosquitoes was reduced 90 per cent., with a corresponding gain to the community in the diminution of mosquito-conveyed disease. The same happened in Panama, Rio and elsewhere.

All water-tanks, gutters, and cisterns must be effectually screened against *Aëdes ægypti* by fine-meshed metallic gauze ; discarded tins should be collected and rolled out by steam rollers ; all puddles and stagnant water must be abolished and all holes in trees should be closed or the trees felled. Roof gutters are best abolished altogether. In Africa special attention must be paid to the control of mosquito-breeding on native dhows. All cases of any kind of fever, no matter how mild they may be, or what their nature, must be reported at once to the central sanitary authorities, who should have full powers promptly to screen or otherwise deal with them and the houses in which they originated. The general use of mosquito-nets must be insisted upon. Adult mosquitoes should be destroyed by swatting, and sprinkling insecticides. The chief substance used in destroying adult aëdes in buildings is *Flit*, which is a mixture of pyrethrum, xylol, cresol, and methyl salicylate in paraffin. A mixture of carbon tetrachloride, 7 per cent., with methyl salicylate, 3 per cent., is also recommended. For other insecticidal sprays, see p. 114.

Any delay in recognizing the earliest cases of a threatened epidemic is, as shown by experience in New Orleans, most dangerous, leading, as it may, to the rapid multiplication of infected centres.

Ships should not be allowed to clear from infected ports, nor to enter non-infected ports, during the hot season, without adequate inspection.

Aircraft.—It is necessary, in view of the increasing facilities of air travel, to immunize all those proceeding from an endemic to a non-endemic area. It has been recommended by the International Sanitary Commission for Aerial Navigation that the measures for preventing spread by aerial traffic should be taken primarily before departure from areas where the disease exists, and only secondarily at ports of arrival. Measures to be taken before departure include freedom of crews and passengers from any risk of infection during six days before embarkation and freedom of aircraft and cargo from the possibility of conveying mosquitoes. It has been laid down that an " anti-amaryl " aerodrome must be situated at an adequate distance from the nearest inhabited centre, provided with a water supply protected against mosquitoes, with mosquito-proof dwellings for passengers and staff. A building-free zone of 440 yards should be maintained round the perimeter of all aerodromes on the main air lines of communication within the endemic areas. Several considerations should modify the tendency to alarmist views of the danger of importing the yellow-fever virus to Eastern countries such as India or China, where the disease is so far unknown, but where climatic and hygienic conditions are favourable to its spread. One of these is the ease with which aerodromes can be kept free from yellow-fever mosquitoes, as well as the ease and rapidity with which aircraft can be freed.

In the United States it has been proved conclusively that *Aëdes ægypti* can be carried by aircraft for long distances, and the necessity of destroying these insects is insisted upon in all aeroplanes flying in tropical countries. Either fumigants or a spray may be used ; among the former, certain preparations of hydrocyanic acid give the best results, and the use of " discoids " (discs of unglazed paper soaked with liquid HCN) or Zyklon (fuller's earth impregnated) is recommended. They cannot, however, be used when passengers are already in the 'plane. Either fumigant or spray can be employed easily and without danger by a skilful fumigator using a hand-spray connected by a flexible tube to a supply of air under pressure. Half an ounce of HCN per 1,000 cu. ft. may be regarded as the maximal dose for killing mosquitoes. The most efficient sprays are those containing a good extract of pyrethrin. " Deskito " and " Shell Tox," pyrethrins in glucose, are non-toxic, non-inflammable and are now being used ; a 1 in 30 dilution of Deskito in water, 150 c.c. for each 100 cu. ft., is necessary. The less accessible parts of the aircraft are fitted with apparatus composed of a system of tubes which carry the spray from the container. Disinsectization can be effectively carried out in 5–10 minutes.

An aircraft should be regarded as infected with yellow fever if there is on board any person who within nine days of arrival had been in a yellow fever infected area.

If a person has alighted from a yellow fever area at a non-infected anti-amaryl aerodrome and is in possession of a certificate from the Health Office of that aerodrome stating that, during his stay, he either remained within the anti-amaryl aerodrome, or, if he went outside it, he did so under such protected conditions as would make it impossible for him to be bitten by mosquitoes, he may be permitted to proceed ; more especially if he has been protected against the disease by a previous attack or by satisfactory inoculation.

There is danger that, with increased motor traffic and better road communications, infected persons will be able to travel from endemic to non-endemic areas in a time well within the incubation period of the disease. All motor traffic from endemic to non-endemic areas has, therefore, to be carefully regulated.

Prophylactic inoculation has been practised since 1931 in West Africa, Brazil, Columbia and South America generally. At first a modified neutropic strain of the virus was used, together with immune human serum, to reduce any risk of producing encephalitis. An injection of immune serum (0·5 c.c. per kilo body weight) was given, and two hours later the virus, in the form of a filtered suspension of mouse brain, was injected subcutaneously. At that time Laigret and other French workers used the neurotropic virus alone, or mixed with egg yolk or bile, but severe reactions resulted and some cases of meningo-encephalitis developed. In 1936 a modified virus was produced by cultural methods ; it possessed considerable antigenic power with low viscerotropism and equally low neurotropism. With the introduction of the egg-culture method, normal human serum was added to suspend the virus. Unfortunately, severe jaundice, resembling infective hepatitis, appeared some three to four months after inoculation in a number of cases. Thereupon serum was inactivated for 30 minutes at 56° C. and it was considered that, by so doing, the danger of conveying some other unknown virus in human serum had been eliminated. During the first six months of 1942, 28,585 cases of jaundice appeared in American troops who had been injected with this yellow fever vaccine prepared by the Rockefeller Institute, and 62 died of acute necrosis of the liver. Similar accidents have supervened after injection of measles convalescent serum and also after whole-blood transfusion, with an incubation period of about 16 weeks. The explanation of the icterogenic property of some normal human sera has now been given by Findlay and Martin[1] (1943), who found that they contain a virus similar to that of infective hepatitis. The agent responsible for the jaundice is present in the nasal washings and serum from patients in the pre-icteric and possibly also in the icteric stage. The addition of human serum has therefore now been omitted and no further cases of jaundice have occurred.

Reaction immediately following inoculation with the attenuated pantropic virus is either lacking or consists of slight headache for forty-eight hours. After immunization, immune bodies appear in the serum from the twelfth to fourteenth day and reach their maximum about the twenty-first. In many, immune bodies are detectable for seven years or longer by the mouse-protection test. It is advisable that the blood of immunized persons should be tested every two or three years and, if necessary, they should be re-inoculated.

A valid inoculation certificate is one certifying that the bearer has been inoculated for the first time more than fifteen days and less than two years previously to entering the endemic zone, or that he has recovered from an attack of yellow fever and his blood contains immune bodies.

On the whole, results have been very satisfactory. Very few deaths from yellow fever have been recorded in inoculated individuals, though not all are equally protected. Briercliffe reported one who contracted mild yellow fever four months after inoculation. Aëdes mosquitoes are unable to take up the virus from the blood after immunization, so that there is no reason why protective inoculation should not be carried out in areas where these insects are present. Mass inoculation is the only practical answer to the jungle yellow fever problem, as was amply demonstrated by the vaccination of over a million persons in Brazil in 1938.

Steps are now being taken by the authorities in British East and West African territories and the Anglo-Egyptian Sudan to ensure that mass inoculation is done, in any specific area, in Europeans and indigenous natives.

Preparation of yellow fever vaccine.—Because the concentration of the virus in tissue culture is never very high, developing chick embryos, about seven days old, are inoculated with tissue culture virus, 17 D, 0·05 c.c. Aqueous-base vaccine is now employed (Hargett). A small hole is drilled through the shell, and after inoculation this is sealed, and eggs returned to the incubator for a further 90 hours. The embryos are then triturated and for each 3 grm. is added 1 c.c. of distilled water. The finely-divided tissue extract is centrifuged for 30 minutes at 3,500 r.p.m. and the supernatant fluid drawn off. The filtrate, which is used for inoculation, usually contains between 1,000 and 10,000 mouse minimal lethal doses of virus per c.c. Yellow fever virus is very labile, and rapidly becomes inactivated in liquid state even when kept in the icebox, but when desiccated in frozen state *in vacuo* it is much more stable. All vaccine preparations are therefore dried in the frozen state and sealed in glass after desiccation. When the residual moisture is low and the material is kept in the icebox, the virus remains active and virulent for years. If, however, the residual moisture is over 5 per cent. the keeping qualities are reduced. This constitutes one of the chief difficulties in the application of the present type of vaccine for large-scale vaccination under field conditions in the tropics. If the residual moisture content should be above the critical level there is always a danger that, during transportation in a tropical climate, the material will become inactivated, and inactive virus will not immunize.

---

[1] Findlay and his colleagues (1944) have now proved that the icterogenic virus in normal human serum is identical with that of infective hepatitis.

Other ultramicroscopic viruses resembling yellow fever.—Several of these viruses have been isolated in recent years in North and Central Africa and in South America. Their exact significance is as yet uncertain.

Durand's virus (virus D) was isolated in Tunis in 1940 and described by Findlay (1942). It is pathogenic for man as well as the guinea-pig. It is widely distributed in other laboratory animals, and in mice it circulates in the blood without any ill effects. It can be cultured on the chorio-allantoic membrane of the chick. The particles of this virus are from 38 to 57 $m\mu$ in size. Whether this virus is widely distributed as a cause of sickness in man or whether it is mainly confined to guinea-pigs remains to be determined.

Bwamba fever (Western Province of Uganda) has been described by Smithburn, Mahaffy and Paul (1941). This disease is characterized by sudden onset, headache and backache. Symptoms subside in about five to seven days. Nine strains of filterable virus were isolated from the blood of as many patients suffering from this illness. It is pathogenic for mice by intracerebral or intranasal inoculation. Guinea-pigs and rabbits are insusceptible. The virus particles are about 118 to 150 $m\mu$ in size. This virus is now more generally known as the West Nile virus and was found by Smithburn and Jacobs (1942) to be more widely distributed in the West Nile area, in the Bunyoro district, and also is active in the Sudan, Uganda, Kenya and in the Congo. As far as at present known, this virus is closely related to the viruses of St. Louis and Japanese B. encephalitis (*see* p. 617), and perhaps also to that of louping ill.

Other similar viruses have been described from Nigeria ("*Kukuruku disease*") as well as from Colombia, South America.

CHAPTER XVII

RIFT VALLEY FEVER

Synonym. Enzöotic hepatitis.

Definition.—An epidemic disease of sheep and cattle in Kenya, caused by a filterable virus which is transmissible under certain circumstances to man. The best account of this disease is by G. M. Findlay (1932).

History.—Rift Valley fever was first described by Daubney, Hudson, and Garnham in Kenya in 1931; possibly the same disease was observed by Montgomery in 1913.

In 1912 a mortality-rate of 90 per cent. was recorded among the lambs born at the Government Farm, Naivasha (at an altitude of 5,500–6,000 feet), while other farms in the Rift Valley also suffered. In July, 1930, another similar outbreak occurred amongst the ewes and newly-born lambs, accounting for 3,600 of the latter, and 1,200 of the former in seven weeks. A high rate of abortion occurred. Focal necrosis of the liver was the chief pathological lesion at autopsy. During the course of the investigation, when the filterable virus was discovered, all four Europeans there employed developed a dengue-like fever with rigors and backache, whilst every native who had been engaged in herding these sheep had been ill for four days with fever and severe pains. A native volunteer was subsequently inoculated with the filtered virus and reacted with an acute attack of fever on the third day after inoculation; his blood was found to be infective to sheep for nine days afterwards. In addition to sheep and goats, cattle were found susceptible and a natural outbreak occurred in these animals at a farm sixty miles distant from the original outbreak.

The virus in blood, preserved in oxalate-carbol-glycerin, was brought to England by Daubney in 1932, was inoculated into lambs by Dalling and found to be as active as in Kenya, with the result that this investigator and his assistant, Hart, soon developed the same dengue-like train of symptoms. Subsequently other laboratory technicians became infected.

Ætiology.—The virus occurs in the blood and appears to be present in the plasma and attached to the blood-cells; it is found in the blood, liver, spleen, and other internal organs, but not in the urine. It may pass through the placenta of pregnant animals and infect the fœtal tissues. The size of the virus particles has been estimated by Broom and Findlay to be between 23 and 35 $m\mu$. When present in plasma, or suspended in physiological saline at pH 7·2, the virus can pass through Berkefeld N.V. and W. candles, as well as through Chamberland L_2 and L_3 candles, without any loss in virulence. Blood preserved in oxalate-carbol-glycerin has retained its virulence for mice when preserved in the ice-chest at 4° C. for eight months. Like that of yellow fever, the virus of Rift Valley fever is sensitive to the hydrogen-ion concentration of the fluid; at pH 8·0 it is destroyed. Mackenzie (1933) succeeded in cultivating the virus without loss of titre in a medium of chick embryo and Tyrode's solution. The character of this virus remains unaltered. It can also be grown on the chorio-allantoic membrane of the developing chick embryo.

Mackenzie and Findlay, by repeated intracerebral passage in mice which had previously received intraperitoneal injections of immune serum, succeeded in producing a neurotropic strain which causes an acute meningo-encephalomyelitis in mice but little or no necrosis of the liver. Similarly, in monkeys and lambs, a fatal encephalo-myelitis follows intracerebral injection.

Apart from the susceptibility of sheep, lambs and goats, the pathogenicity of the virus for man and monkeys (*Macaca*) and many small rodents (mice, field-mice, wood-mice, hamsters, dormice, and rats) is noticeable. Mice succumb in two to four days. Cats appear to be slightly susceptible. Indian and South American monkeys of the genera *Macaca, Hapale* and *Cebus*, are relatively susceptible, but African monkeys of the genera *Cercopithecus* and *Cercocebus* are relatively insusceptible, and do not suffer from any febrile reaction. Local East African rodents have been found by Daubney and Hudson to be highly susceptible to this virus, and probably play a part in its dissemination. These are *Arvicanthus abyssinicus, Mastomys coucha*, and *Rhabdomys pumilio*.

Using a mouse-protection test somewhat similar to that used in yellow fever, Findlay, Stefanopoulo and MacCallum have found that immune bodies can be detected in the blood of natives from the Nuba Mountains in southern Anglo-Egyptian Sudan, northern Uganda, and French Equatorial Africa; no immune bodies were found in bloods from West Africa.

Duration of infectivity.—In susceptible animals the infection can be transmitted by subcutaneous, intraperitoneal, intratesticular, or intracerebral inoculation, by application to the scarified skin, or by instillation into the nares or conjunctival sac.

In human cases which have been tested, the virus can be demonstrated in the blood for six days after the first rise of temperature, or nine days after the inoculation.

As in yellow fever, it is probable that the apparent disappearance of virus from the blood and tissues is due, not to the death of the virus itself, but to its neutralization in the presence of immune bodies.

Pathology.—The pathological change in animals consists of a focal necrosis of the liver. These foci may be discrete, as in sheep or goats, or may coalesce so as to involve the whole liver, as in young lambs, and in mice, rats and other rodents. The histological changes consist of an infiltration with mononuclear and polymorphonuclear cells, and a hyaline degeneration of the cytoplasm of the liver cells (Councilman lesions). In the livers of infected mice, acidophilic inclusions (or intranuclear bodies) have been found, by Findlay, as in many other filterable virus diseases, and similar bodies have been described by Daubney and Hudson in the livers of experimentally-infected sheep in Kenya. The nuclear changes in the affected cells are of the type known as "oxychromatic degeneration."

Symptoms.—In those cases which have been observed in man, the incubation period varied from four and a half to six days. At the commencement of the fever a feeling of nausea and a sensation of fullness in the hepatic region is experienced, and this is followed by violent headaches, pain in the back, rigors, and general malaise. The face is flushed, and there is photophobia without, however, any marked conjunctival congestion. The tongue is thickly coated and epistaxis usually occurs. Bone pains are confined to the shoulders, back, and legs. The temperature varies between 101° and 102° F. On the fourth day of the fever the temperature falls to normal, accompanied by profuse sweating; a post-febrile weakness and a tendency to sweating on the least exertion remain. The bowels are usually constipated and the urine is deep yellow. There appears to be an initial slight leucocytosis, followed on the third and fourth days by a definite leucopenia, which persists into convalescence.

One human case has been recorded in which the fever lasted for ten days, ranging from 101°–103° F., and showed a regular saddle-back character. The virus of Rift Valley fever thus produces in man a disease resembling in many respects dengue and phlebotomus fevers. In one instance three febrile attacks of decreasing severity were noted. One fatal infection in man was recorded by Schwentker and Rivers (1934) from the Rockefeller Institute, New York. This occurred in one of the members of the staff who had been working with the virus. Although the course of the illness was otherwise typical, it was complicated by thrombo-phlebitis—a condition not previously described in association with this disease—and death was due to a pulmonary embolus. In the early stages the virus was present in the patient's blood and was pathogenic to mice. Death occurred on the forty-fifth day of the illness.

Immunity.—An immunity can be established in infected monkeys and it has been shown that they cannot be re-infected with massive doses of the virus for at least six months. In man immunity is present for at least seven years.

Diagnosis.—The virus of Rift Valley fever is distinguished from that of yellow fever by its pathogenicity on intraperitoneal injection for small rodents (mice and rats), and by the fact that monkeys (*Macaca*) immune to yellow fever are later susceptible to infection with the virus of Rift Valley fever. Human cases have also occurred in persons known to have suffered from yellow fever. The serum of recovered cases gives a specific complement-fixation reaction, and contains immune bodies which neutralize the virus when serum and virus are inoculated into mice. There is no relationship with dengue, phlebotomus fever, or psittacosis.

Treatment.—In human cases, treatment by injection of immune serum has been attempted by Findlay, though it is not possible to estimate the result. In view of the toxic action on the liver, glucose should be given by mouth.

Prophylaxis.—Evidently in the midst of a sheep epidemic human beings are themselves very susceptible to infection. There is some evidence to show that in the Naivasha district of Kenya, a mosquito—*Mansonia fuscopennata*—may be responsible for the transmission of the virus, whilst Daubney and Hudson now report that it is possible to convey the disease by inoculation of the body-contents of other mosquitoes, such as *M. versicolor* and *M. microannulata*. The neurotropic virus may be of value in immunizing sheep and cattle, since on subcutaneous injection it causes almost no reaction.

CHAPTER XVIII

PSITTACOSIS

Definition.—A disease of parrots, communicable to man, and occurring naturally in finches, fulmar petrels and other birds.

History.—The first definitely recognized epidemic of psittacosis occurred in Ulster in Switzerland in 1879, and there were seven cases with three deaths in the house of Dr. Ritter, where there were sickly parrots and some other birds. In 1882 there was a further small outbreak in Berne. In 1892 a large outbreak occurred in Paris, in which successive cases of pneumonia coincided with an importation of parrots from Buenos Aires. The homes of the two men who had imported the parrots became foci of human infection, one giving rise to 22 cases and 6 deaths, the other to 25 cases with 7 deaths. Dujardin Beaumetz reported that the human cases resembled influenzal broncho-pneumonia. Subsequently other fatal cases occurred in which the association with sick parrots was obvious, and Nocard isolated a bacillus allied to the paratyphoid group which was thought to be the ætiological agent of the disease. The Paris outbreaks smouldered on till 1897, when a somewhat limited one occurred in Italy, which was again traced to importation of Amazon parrots from Buenos Aires.

The first big outbreak of psittacosis in Germany occurred in Cologne, in 1898, and there was a distinct association with diseased parrots. The disease had also been met in the United States since 1904. In 1917 an epidemic occurred in Pennsylvania in a store in which a number of sick parrots were kept. In England, before the epidemic of 1929-30, only six cases had been reported. It was in the course of this epidemic that the erroneous hypothesis of a Salmonella infection was abandoned and the true ætiology of a " filterable virus " established by Bedson, Western, and Levy Simpson. An epidemic among the personnel of the London Zoological Gardens in 1938, which resulted in five cases and one death, was due to the importation of parrots from the New World.

Epidemiology.—Recent outbreaks of psittacosis were at one time thought to have all arisen in Brazil, but no human cases have ever been reported in that country. There is no evidence that epizöotics of this disease occur under natural conditions amongst the parrots in the forests of Brazil, but when these Amazon parrots, especially *Amazona æstiva*, are in captivity, and are transported under grossly insanitary conditions to Europe, the disease arises and is able to spread.

A greater mortality from this disease occurs during the cold weather, as found by Gordon in budgerigars experimentally inoculated with psittacosis virus. The symptoms in birds are those of an acute infection. The infected bird sits listlessly, with ruffled and dirty plumage; it suffers from diarrhœa and there is usually a discharge from the eyes and nostrils. Recently, however, the problem has been further complicated by the discovery of the virus in apparently healthy birds in California and in Australia, by Bedson, Meyer and others. When killed, they are found to have enlarged spleens containing the virus.

The source of infection is usually the Amazon parrot, though grey African parrots have been the apparent cause in some of the British cases. In Australia a number of parrots caught in New South Wales have been found infected, while in the Northern Territory the Gouldian finch (*Polphila gouldiæ*) and the long-tail finch (*P. acuticauda*) carry the virus. The Bengalese finch, a hybrid between *Aidemosyne malabarica* and *Uroloncha striata*, imported from China, is also a carrier, as are the siskin and crossbill. Among the *Ploceidæ* the Java sparrow may show infection.

Possibly canaries, blackbirds and thrushes may occasionally act as carriers, and a disease resembling psittacosis has occurred in the Faroe Islands, where apparently it is propagated by the fulmar petrel, *Fulmarus glacialis* (Haagen and Mauer). During the last few years an atypical pneumonia has been described from these islands. It is confined to the middle-aged and occurs in summer and early autumn. Infection appears to be contracted by the women who pluck and salt down the fulmar fledglings. (Rasmussen, 1938).

The virus has been found to cause disease in pigeons in South Africa and in the United States, where at least five human cases have been reported in those who have had contact with sick birds. Andrewes and Mills (1943) isolated the virus from apparently normal pigeons in Southern England. It is not possible to tell from the appearance of the bird whether it is infected or not.

Parrots may remain in a subacute infectious condition for several years. Direct infection from man to man has been noted, and in one English outbreak the doctor in attendance contracted the disease from his patient. House epidemics, too, are apparently not uncommon, particularly in Vienna, and, according to Gerlach, human beings may act as virus carriers after imperceptible infections.

An infective pulmonary condition with a general typhoidal picture occurring in definite groups should suggest psittacosis.

Ætiology.—The virus nature of psittacosis was worked out by Bedson and Western on the budgerigar (*Melopsittacus undulatus*), in which the disease is highly contagious. The virus can be transmitted by citrated blood or emulsions of liver or spleen. The blood contains the virus in the early stages of the disease and as long as the tenth day. Besides parrots and parakeets, hens are susceptible. Mice are susceptible to experimental infection by intraperitoneal inoculation and, on intracerebral injection, develop encephalitis. These animals become acutely ill three or four days after injection and die of septicæmia with enlargement of the spleen.

The virus of psittacosis will pass Chamberland's L_1, L_2 and Seitz EK filters. The size is 220–330 $m\mu$. The amount inoculated into mice is 0·5 c.c. intraperitoneally. Rabbits and guinea-pigs are susceptible to intracerebral inoculation (Rivers and Berry), as is also the Tasmanian devil (*Sarcophilus harrisii*). The virulence of the virus is increased by passage through mice, and an intracerebral inoculation reveals a definite neurotropic tendency (Gordon). The virus of psittacosis inoculated intratracheally or intranasally in monkeys produces a pneumonia similar to that observed in man (Rivers and Berry).

In parrots which have succumbed to a fatal dose of the virus, minute bodies are seen in the endothelial leucocytes in and near focal lesions. These Gram-negative bacillary bodies have also been found in human tissues and have been described by Levinthal, Coles, and Lillie as *Rickettsia psittaci*. The forms described in the early stages of infections of the mouse with psittacosis are developmental stages of the virus, which, according to Bedson and Bland, has a complicated life-cycle reminiscent of certain of the protozoa. These virus bodies, readily demonstrated by Giemsa's and Castañeda's stains, show considerable morphological variations. Some forms resemble bacteria; others rickettsiæ and, indeed, some authorities (Lillie) think the virus belongs to this group.

Pathology.—The pathology of psittacosis in the parrot was described by Lillie. A fibrinous or purulent pericarditis is produced with pericardial hæmorrhages. The liver is usually enlarged and studded with white foci of necrosis with red areolæ. On microscopic section this organ showed coagulation necrosis with oxyphil, pyknotic and karyolytic liver cells. Marked proliferation of the Kupffer cells was noted, and focal infiltration by plasma cells and macrophages laden with fat.

Autopsy findings in man are those of a general septicæmia with inflammatory condition of the lungs. The spleen is normally enlarged and soft, with semi-diffluent pulp. The most striking changes are found in the lungs, which exhibit a peculiar hæmorrhagic vesicular pneumonia, complicated by pulmonary thrombosis and a mucopurulent bronchitis in which bacteria are numerous. In the microscopic pathology one of the most striking features of psittacosis-pneumonia is the variation in type of the alveolar contents, often within the same microscopic field. Some alveoli contain serum alone ; some serum and red corpuscles, and some leucocytes, macrophage cells and alveolar epithelium. An interstitial cellular infiltration has been noted in about half the cases.

The lung changes were at first thought to resemble those of influenzal bronchopneumonia, but they are now recognized as a distinct type. In psittacosis the consolidation is of a lobar type with abundant fibrin formation throughout the affected areas ; there is practically no polymorphonuclear reaction, and hæmorrhages occur only in relation to the more severely damaged areas. The bronchioles are involved. (In influenza the process is essentially a bronchopneumonia and the lung is nodular.) In the brain a condition known as " cerebral purpura " is not uncommon, caused by masses of red cells escaping by diapedesis from the capillaries, the walls of which remain intact.

Symptoms.—Psittacosis in man is a severe illness with a high mortality (about 20 per cent.). All ages and both sexes are affected. It is, however, as a rule, comparatively mild in young people, increasing in severity with age. In those over fifty it is usually fatal. The duration of the disease is two to three weeks. Convalescence is protracted and tedious, and may be interrupted by temporary relapses or by femoral-vein thrombosis.

During the first week the patient may feel comparatively well, in spite of high pyrexia. The early symptoms are epistaxis and generalized pains. Towards the end of the week the whole aspect becomes more severe ; the patient suffers from profound exhaustion and tends to become somnolent and intermittently irritable ; there is usually a troublesome paroxysmal cough, which persists to the second week. Scattered signs of consolidation, which may eventually involve the greater part of the lung, become apparent. Constipation now becomes manifest and gives rise to tenesmus and abdominal discomfort. During the second week a state of semi-coma with muttering delirium sets in, to such an extent that life is despaired of, but when things appear at their worst, the temperature begins to fall by lysis, and in a few days the patient gradually shows signs of improvement.

Although the illness is usually severe, yet mild and even ambulatory cases have been recorded. The incubation period appears to be about eight to ten days, but may extend to sixteen days. In man-to-man infections it is generally about four days. Pyrexia is usually of the typhoid type, and occurs in all cases ; some have a gradual rise of temperature of the " step-ladder " variety.

Epistaxis is early, usually on the first, sometimes as late as the eleventh to fourteenth day. Headache is a constant feature. Chills and rigors usually occur, and with the latter a temperature of 104° F. has been noted. Generalized influenza-like pains are the rule. The throat is usually sore and congested, and in a few cases the tongue is swollen and sore, in the condition known as " peribuccal œdema." The lungs are involved in almost every case, with a cough of varying intensity, but the sputum is scanty ; it may be rusty, characteristic of lobar pneumonia. The physical signs in the lungs vary considerably. A relative brachycardia is the characteristic feature of the cardiovascular system. With a temperature of 103° F. the pulse is about 90 and this feature increases the typhoidal-like character of the disease and, indeed, the typhoid state accompanies all severe cases. Photophobia is also a feature, and, towards the end of the first week, most patients become lethargic, with stuporose appearance, sluggish speech, and blunted mentality.

"Rose spots," or similar skin lesions, have been noted in nine British cases, at varying periods from about the seventh to the thirteenth days. The spots were on the chest and abdomen, more rarely on the back, measured 2–4 mm. in diameter, and faded on pressure. Parotitis has been noted twice. The blood picture in characteristic psittacosis is not markedly altered. Ambulatory cases may have a fatal relapse.

Diagnosis.—On clinical grounds the diagnosis of psittacosis is not easy, as it has many features in common with typhoid. The gastro-intestinal symptoms may resemble those of that disease, but perforation and hæmorrhage never occur. The spleen is usually palpable in typhoid, but in only two out of 80 cases of psittacosis has this been recorded. With influenza, too, it has many features in common. Blood-cultures and agglutination reactions are completely negative in psittacosis, and inoculations of blood or sputum in the early stages of the illness will prove fatal to mice. Apart from isolation of the virus, the most satisfactory method of diagnosis is by the complement fixation reaction. According to Bedson, the most satisfactory antigen is obtained from the spleens of infected mice, as it is essential to employ material that is rich in it. Antigen may also be prepared from cultures of the virus on agar-serum or chick-embryo medium. The technique is similar to that of the Wassermann reaction. It is diagnostic 8–12 days from the beginning of the disease, when it occurs 1 in 2–1 in 8 and in higher dilutions. There is a non-specific fixation with syphilitic sera up to 1 in 8.

Differential diagnosis.—Psittacosis in parrots has to be differentiated from Pacheco's parrot disease, which was discovered by Pacheco, Bier and Meyer while investigating pathological conditions of parrots in Brazil. The filterable virus produces a clinical picture similar to psittacosis; it differs from psittacosis virus in not being communicable to man or pathogenic to mice, while in the necrotic liver cells there are large acidophilic intranuclear inclusions.

Prognosis.—The mortality rate in human cases so far reported is high—usually about 20 per cent.—and convalescence is slow and tedious.

Treatment.—Symptomatic treatment and nursing should be on similar lines to those of typhoid. The only treatment which might be of any value is early use of serum of patients who have recovered from the disease. Injections of non-specific human serum appears to produce good results in some instances, while prontosil has been tried with good results in one case.

Prophylaxis.—The best method of avoiding a disease which is conveyed by birds of the parrot family is to avoid contact with these birds. Petting parrots, and especially insertion of the beak into the mouth, should never be allowed. The importation of members of the parrot family and finches into countries where the disease is not endemic should be prohibited.

CHAPTER XIX

RABIES

Synonyms. Hydrophobia; Rage (French); Tollwut (German); Lyssa; Rabbia (Italian).

Definition.—Rabies is a disorder of dogs and other animals. Under natural conditions it is transmitted both to animals and man by inoculation of virulent saliva in the act of biting.

It is now realized that it is caused by an ultra-microscopic virus, which invades the central nervous system by the peripheral nerves, and becomes fixed there. The incubation period is in some cases very long, and the centres for respiration and deglutition in the brain are severely attacked, so that spasm and, eventually, paralysis result. Protection is afforded by inoculation with attentuated or killed rabies virus and, to some extent, by antirabic serum.

History.—The earliest recognizable reference to rabies is that of Aristotle in the fourth century B.C. The first extensive descriptions are those of Celsus in the first century A.D. and Cælius Aurelianus and Galen in the second. The paralytic form was first recognized by Van Swieten in 1771. The first demonstration of the identity of the disease in man and animals was made by Magendie and Breschet. The modern study of the disease dates from the classical work of Pasteur, who devised the method of subdural inoculation of material from the central nervous system, and laid the foundations of the preventive system of antirabic inoculation which bears his name. He also suggested that the causal agent might be an invisible microbe.

Geographical distribution.—There is no part of the earth where man and other terrestrial animals can live where rabies cannot potentially exist. It occurs quite commonly in Greenland, Iceland and other Arctic countries, but it is possible that in the Far North a special modified form exists. In the tropics and subtropics, especially where jackals and wild dogs abound, a specially virulent form is sometimes prevalent. In South America and in the West Indies, cattle are commonly affected[1], constituting a reservoir of the virus, and in Jamaica the vampire bat plays an important part in dissemination. Australia is said to be free from this disease, and this freedom is ascribed to the peculiar fauna and the rigid quarantine which has been imposed upon dogs.

Rabies has been stamped out from Great Britain for nearly forty years, except for a small outbreak among dogs when an animal was smuggled into the country by aeroplane. It is very prevalent indeed in India, where, on account of the numerous and dangerous bites from wolves and jackals, it causes a high mortality. Statistics are difficult to obtain, but an average of about 5,000 persons is treated annually at the Pasteur Institute, Kasauli.

In the United States of America 10 states or territories are considered to be free from the disease both in man and animals, and until recently it accounted for about 100 deaths a year.

Animals susceptible to rabies.—All warm-blooded animals are susceptible, under favourable conditions, to experimental inoculation of the rabies virus; it is more commonly met in nature in those mammals which are subjected most often to the bites of dogs, wolves and foxes. Some species are seldom infected, either because they are seldom subjected to bites, or because they are provided with thick fur.

---

[1] In South America rabies in cattle is—perhaps wrongly—termed "Mal de Caderas."

There is some reason to believe that skunks, weasels and stoats, and possibly the meerkat (*Cynictis penicillata*) may propagate the disease widely among their own kind, as does the dog. The susceptibility of rats to subcutaneous inoculation led to the opinion that these animals might also be capable of perpetuating this disease in nature, but of this there is little evidence. In South Africa meerkats act as a reservoir, while in the United States grey squirrels may play a similar rôle.

Domesticated animals are affected with the following percentage frequency: dogs 85·1; cattle 10·7; horses 1·48; swine 1·12; cats 0·81; sheep 0·7; goats 0·09. Donkeys are rarely affected.

Wolves, foxes and rabbits may be affected in countries where they abound. Birds are relatively insusceptible to inoculation and this is said to be due to their high body temperature. Frogs are said to be susceptible.

The alleged disproportionate prevalence of rabies during certain seasons of the year appears to have little foundation in fact.

Ætiology.—The symptoms of rabies indubitably point to an intoxication of the nervous system, while the pathological changes also indicate that this is the part affected.

The most generally accepted view of the infection is that the virus of rabies, upon its introduction beneath the epidermis, finds its most favourable medium for propagation in nerve-endings and fibres torn in the region of the bite. Along the course of the axis cylinders it develops and travels, without disturbing their function, until the central nervous system is reached. The virus is strictly neurotropic, although Marinesco and Stroesco consider that the main path of dissemination is by the lymphatics. Finally, the cells of the central nervous system are attacked, the first effect being excessive stimulation, followed by destruction. At the same time a neurotoxin is produced which is responsible for some of the symptoms. Nerves leading from the site of the inoculation to the central nervous system have been shown to become progressively infectious in ascending segments, while complete section previous to inoculation confines the toxin to the lower segment. The blood and lymph appear to be incapable of taking up the toxin from the site of inoculation.

Street virus ("*virus des rues*," "*Strassenvirus*") is the strain found in the virulent nervous tissue infected by the natural disease[1]; its virulence is very variable and, when inoculated subdurally into rabbits, it causes symptoms of rabies after a variable period of more than fourteen days. Inoculations should, if possible, be carried on for several passages, till the nature of the virus becomes clear. Considerable variation in street virus occurs, some strains showing rapid adaptation to the central nervous system.

Fixed virus (*virus fixe*) is modified from the street virus by passing through a long series of rabbits. In this manner its virulence becomes greater for these animals, so that finally they develop the disease after a constant or "fixed" period of inoculation, after which no further *passages* can reduce the incubation period below this span. The mouse, however, appears to be the most suitable animal for rapid diagnosis.

Nicolau and Kopciowska were able to pass a strain of rabies virus from sciatic nerve to sciatic nerve for more than one year, and have thereby reconverted "fixed virus" into "street virus." The strain of fixed virus has been passaged in the laboratory for six years and gives rise to from one to four Negri bodies

[1] The disease known as *Oulou-fato* among the natives in West Africa has been shown to be identical with rabies. Nicolau, Mathis, and Constantinesco claimed that this virus is less virulent, and more difficult to fix, than is the true rabies virus.

in 100 ganglion cells of the horn of Ammon. This transformation was achieved by passage inoculations made into the right sciatic nerve, the emulsions employed being obtained from the *left* sciatic nerve of the previous animal. With great trouble, two lines of *passage* have been obtained covering a period of more than a year.

Negri "bodies."—Negri originally described certain oxyphilic granules in the nerve-ganglia cells of the *hippocampus major.* Although they are probably of the same nature as the cytoplasmic inclusion bodies found in association with other ultramicroscopic viruses, yet Negri bodies are admittedly very constant in rabies, peculiar to it, and useful for diagnosis. Recent ultrafiltration methods (Galloway and Elford, 1936) have made these bodies more easily visible.

Covell and Danks, after micro-incineration and other studies, concluded that the Negri bodies arise from constituents in the nerve-cell as a result of the virus. They are not present in every case of rabies, but when a person has been bitten by an animal having symptoms suspicious of rabies, preventive treatment should at once be instituted. Inoculation tests have shown that this practice is sound. The custom of killing suspected animals immediately after they have bitten their victim is not recommended, as this practice operates against the demonstration of Negri bodies which may be present in the later stages of the disease. Other changes in the nervous tissue, of less importance from a diagnostic view, have been described, and Courmont and Lesieur claimed that in the dog there is a relative polymorphonuclear-leucocyte increase in the blood and in the lungs; whereas in the normal dog these cells average 53 per cent., in the rabid animal they form 90 per cent.

Passage of virus in carnivorous animals.—When passed through dogs the virus does not lose its potency; on the contrary, it becomes fixed with an incubation period of eight or nine days, but in rats *street virus* becomes rapidly augmented in virulence; on the other hand *attenuation* and, finally, *loss* of virulence is produced when monkeys, frogs and birds are inoculated.

Location of the virus in the body.—The central nervous system and the peripheral nerves contain the virus with constancy, but infectiousness is variable in different parts of the nervous system. It was found by Nitsch that 0·1 mgm. of the brain cortex (*fixed virus*) was lethal to rabbits in seven to nine days, whilst 0·5 mg. from the centre of the cord was not virulent, though 1·0 mgm. was. The medulla, for instance, is five times more virulent than the rest of the cord. The salivary glands of dogs are constantly infectious. The generally accepted view is that the virus finds its way to these glands by way of the nerves and, according to Remlinger, the saliva of a dog may remain virulent five days after apparent recovery from rabies. In man the salivary glands are seldom invaded. The blood is non-infectious, either in man or in experimental animals. There is no evidence that the virus can be conveyed to the fœtus. Neither the milk, urine, liver and spleen, nor spermatic fluids ever harbour it.

Cultivation of the virus.—Although there is considerable doubt whether the virus can be successfully grown in the chorio-allantoic membrane of the developing chick embryo, it has been grown successfully, either in a plasma medium or in serum-Tyrode, containing mouse- or chick-embryo tissue. Human and simian are more satisfactory than rabbit serum for this purpose.

Properties of the virus.—The particle size of the virus of fixed rabies is 100–150 $m\ \mu$, as determined by filtration. Centrifugalization renders the supernatant fluid of an emulsion avirulent. The virus is sensitive to heat; thus ordinary undried emulsions lose virulence after exposure to 50° C. for sixty minutes and to 60° C. for thirty minutes. In the dried form, however, the virus resists 105° C. for two minutes. On the other hand it can withstand intense cold (liquid air at —190° C.) for three months, and 50 per cent. glycerin for many months.

Desiccation.—Rapid desiccation of brain and spinal cord is not destructive to virulence, and virus in this state can be preserved in stoppered bottles in the dark for nine months. Gradual desiccation at higher temperatures (23° C.) is accompanied by gradual attenuation, so that virulence is usually lost in five or six days.

Filtration.—Emulsified rabies virus passes through the pores of Berkefeld filters, but not finer than L_3 in the series of Chamberland bougies, and it is claimed that fixed virus passes through finer pores than street virus.

Chemical agents.—Rabies virus is sensitive to the action of acids and alkalis, but more resistant to chemical disinfectants than are bacterial emulsions. Probably, when it is introduced into the subcutaneous tissues, leucocytes and other cells are capable of absorbing it. The serum which is immunized against rabies is able to destroy the activity of the rabies virus *in vitro.* From immunized sheep a serum of a very high antitoxic titre has been obtained.

The Trinidad disease (Paralyssa).—Hurst and Pawan (1930) described a curious paralytic form of rabies in Trinidad. It appears to affect and be spread by the vampire bat, which in South America and in the Antilles feeds indiscriminately on the blood of man and cattle. The disease was first noticed in cows; subsequently five cases were discovered in man, and the virus was transmitted to monkeys. This disease is apparently identical with "mal de caderas" of South American cattle, but is probably better termed South American *lyssa.* Some doubt has been expressed whether the bat at first identified by Pawan was the vampire or a harmless species of the genus *Artibœus,* but Lima (1934) in Brazil, by direct experiment, brought forward evidence that, in the State of Santa Catherina, epizöotics of paralyssa are prevalent in the favourite haunts of vampire bats (Desmodidæ) and that the transmitter is the local species (*Desmodus rotundus*). The virus may be demonstrated in their saliva and they act as carriers for considerable periods. Kraus and Duren suggested the designation "*Paralyssa*" for this form.

Incubation period of rabies.—This is remarkable for its length and great variability. In nature it is seldom under ten days, but may extend to a year, or even longer, though in the majority of cases the disease develops before the end of the third month.

The length of the incubation period is influenced by the following factors. (i) The species of animal: it is usually longer in man than in the lower animals. (ii) The site of the inoculation: the shorter the distance from the brain, the shorter will be the period of latency, whilst females exhibit a shorter period than males, and children than adults. (iii) The severity of the wound and the physical condition of the patient have an undoubted influence.

Symptoms and clinical course.—Rabies presents two distinct clinical types: the furious or excited, and the quiet, "dumb" or paralytic. Some distinguish four types of the disease: cerebral, medullary, cerebellar and sympathetic.

The excited or furious type.—The onset of rabies is usually rapid; the patient shows some psychical change very early, becoming anxious, melancholy, and possessed of strange presentiments. Sleep becomes impossible. Soon, local numbness, twitching, and a sense of itching progress from the wound, which becomes engorged and tender. Sometimes the first symptom is a strange sensation in the throat or a sense of constriction of the fauces.

The mental symptoms may be purely hysterical, and many cases have been recorded in which the onset is determined by mental shock, though fright and terror may be regarded as manifestations of the disease. An initial rise of temperature is perhaps the most constant early sign.

Symptoms may last several days before the outbreak, but usually only twenty-four to forty-eight hours. *Hydrophobia*, the outstanding symptom, prevails in the great majority, and arises from extremely painful spasms of the organs of deglutition and respiration induced by attempts to eat and, especially, to drink. These spasms are so agonizing that they exceed, possibly, all other forms of human suffering; the sight or smell, or even the sound of liquids, is sufficient to excite an attack. When an effort is made to gulp down a small quantity of liquid it is expelled, with an anguishing spasm of the throat and larynx. This condition is a state of hyper-susceptibility of the nerve-cells to external stimuli. Draughts of air may bring on a convulsive seizure; skin and tendon reflexes are exaggerated; respiratory spasms involve the thoracic muscles and cannot be relieved by intubation. Solid foods are usually more readily taken than fluids.

The disease progresses rapidly. In the majority of instances there may be periods of latency which cause hope of recovery and doubts of the diagnosis. The mind is usually exceptionally clear, questions being answered with intelligence until the voice becomes indistinct and words unintelligible. But there are periods of excitement which may be truly maniacal; the patient may injure or destroy any objects near at hand, but there is seldom any tendency to injure other persons. Sexual excitement, accompanied by priapism, is frequent. The voice usually becomes hoarse; the strange sounds emitted during expectoration at the onset of the seizure have given rise to the popular conception of "barking like a dog."

The convulsive seizures become more and more pronounced until paralysis leads to death. The muscles, which have been racked to the limit of endurance, become limp, and the face, previously expressive of terror and suffering, becomes expressionless. There is usually an excessive secretion of ropy saliva, which the patient is unable to expel. Finally, the breathing becomes irregular and feeble and at last ceases altogether. The temperature rises before death. Sugar and acetone are usually found in the urine. In the paralytic stage the pupil is dilated.

The paralytic type in man.—Because symptoms are less marked than in the violent type, this undoubtedly remains unrecognized in many cases. For a time the mere existence of this form was forgotten. Pathologically it has been attributed to infection with a large amount of virus and to the involvement of the spinal cord rather than the brain. The onset takes place with high fever, general malaise, headache, and vomiting; afterwards there is localized pain, especially in the bitten parts; a heaviness and numbness of these regions follow, then ataxia, weakness, and finally paralysis. Girdle sensation is usually present. Consciousness is retained until late in the disease. Paralysis spreads, with preceding or accompanying pain in the affected parts, involving limbs, trunk, rectum, bladder, face, tongue, and eye muscles. Some difficulty in swallowing liquids results from the respiratory embarrassment, but "hydrophobia" is usually absent. Frequently, normal respiration may be temporarily restored and death takes place from cardiac paralysis. This form of the disease is more prolonged than the furious type, lasting up to seven and a half days, as compared to the average duration of three to four days in the latter.

Rabies in the lower animals.—On account of its highly developed intelligence the dog shows the most marked psychical disturbances, and when it begins to exhibit marked and causeless changes in disposition, suspicion of rabies should be entertained, especially if there are other reasons. The dog may become more morose, sullen, or irritable, or show excessive affection. Fatal infections are apt to occur at this stage through licking wounds or abraded surfaces.

A very characteristic symptom is the change in the character of the voice, which is said to resemble the yelping of a tired foxhound giving tongue. The rabid dog is easily startled, growls or barks on the slightest provocation, and may bite other animals, or man; he bites them, or passes by, but never swerves to attack them.

The popular idea of a rabid dog as an aggressively mad animal is incorrect. On the contrary, it looks ill, takes no interest in its surroundings, trots along with a wavering gait, often with unilateral drooping of the ear. Convulsions soon appear and the animal may die during one. More frequently, a paralytic stage supervenes and the dog drags itself to a secluded spot. In contradistinction to its usual habit, it swallows sticks and stones and other objects. Swallowing, at first difficult, later becomes impossible.

The *paralytic form* is most frequent amongst dogs, and is peculiarly dangerous to man. The dog becomes the object of sympathy so that bystanders often become scratched or bitten. Such rabid dogs are intensely thirsty and have no fear of water but, owing to the paralytic condition of the throat, they are unable to swallow. Glycosuria is a common symptom of rabies in animals, and is said not to be of renal origin.

The paralytic form is very common in herbivora, but horses present the most agonizing type of the furious form.

Experimental rabies in the rabbit.—After subdural inoculation, rabies manifests itself by a premonitory fever; the animal appears sleepy and does not eat. The appearance of the face is characteristic; the eyes have a staring expression and frequently there is drooping and lopping of one ear. The animal urinates more frequently than normal. Rarely, the furious stage supervenes, convulsive seizures are frequently observed and there is grinding of the teeth. Paralysis begins in the hind legs and proceeds forwards. Abortion is common in pregnant females.

Immunity.—Natural immunity to rabies is exhibited by a number of lower vertebrates; occasionally in mammals an *individual immunity* may be observed, and a state of *hereditary immunity* has been described by Remlinger and Konradi.

Much more is known about acquired immunity. Man and animals may be rendered immune by inoculation with modified virus of rabies; secondly, their blood acquires "rabicidal" properties, that is, the power to render inert the virulent material exposed to its action *in vitro.*

Immunity to rabies can be conferred by increasing doses of filtered emulsions, especially those exposed to high temperatures.

Levaditi and Stoel showed that the virus of rabies is maintained, and probably multiplies, when placed *in vitro* in contact with cellular elements. The virus develops in contact with embryonic cerebral tissue *in vitro.*

The virus is more virulent in rabbits, inasmuch as it causes the disease more rapidly, but at the same time it loses virulence for animals higher in the taxonomical scale. It is assumed that, by passage through rabbits, the virus becomes augmented, hence the early onset and the paralytic symptoms. Its resistance to the inimical action of the body juices is thought to be reduced; hence the harmlessness of subcutaneous injection. The argument in favour of the toxin of rabies being an ultramicroscopic virus is the production of symptoms of fever, emaciation, and cachexia after passage through a filter. Glusman, Solonjowa and Predtetschenkaya have found that the virus can pass through Chamberland bougies L_2 and L_3. Occasionally during inoculations, or soon after, paralytic symptoms appear, apparently not directly due to rabic infection. Paralysis of the Landry type is often noted. These paralytic accidents are occasioned, it is believed, by some toxic substance present in nervous tissues derived both from rabid and normal animals.

There are other peculiarities of the rabies virus toxin; thus, the spinal cord of the rabbit, when dried until it has lost its infectiousness, has also entirely lost its immunizing properties. It is therefore possible to explain artificial immunity conferred by injection of *fixed virus.* The successive injection of dilutions of fixed virus, increasing from weak to strong, or of emulsion of the dried cord has the following effect: the rabies toxin contained within them arrives earlier at the cells of the central nervous system by way of the blood and lymph circulation than it does by progressing along the nerves, so that when it arrives at the centres, the protoplasm of the cells has already become accustomed to the action of the rabies toxin; consequently the virus, introduced during preventive inoculation, can no longer affect them and produce chromolytic changes. Unattenuated "*fixed*" *virus* may now be used for production of immunity, for there is no danger of producing rabic infection from its *subcutaneous* injection. It has recently been shown that, in the presence of a pointolite, rabies virus may be inactivated by the photodynamic action of dyes, such as methylene blue or proflavine in high dilutions. Inactivated virus, however, retains its antigenic power.

Diagnosis and differential diagnosis.—The diagnosis of rabies rests upon the consideration of many factors, such as the history of exposure to infection, the length of the period of incubation, the clinical symptoms and course, the termination, and the post-mortem findings, confirmed by inoculation tests on animals.

In recounting the history of exposure to the virus, due consideration must be given to the mental excitement of the patient and to the fact that the rabies may be infectious several days before the appearance of rabid symptoms in infected animals.

Very often it happens that no history of infection may be obtained until late in the disease, or until after death. There are instances where the victim has died of rabies, yet the infecting dog has recovered. In assessing the length of the period of incubation, well-authenticated cases of rabies may commence as early as ten days after exposure, but hysterical manifestations come on a few hours or days after assumed exposure. The mental behaviour of the patient during the probationary period may assist in diagnosis, but many cases show no disturbance whatever until tell-tale signs develop. The chief difficulty is, of course, with hysterical manifestations, and it is stated that hypersensitiveness to draughts of air, common in true rabies, is not evoked in hysteria, so that fanning a patient may produce a convulsive seizure. Tetanus and mania may also simulate rabies. The absence of trismus in one, and of convulsive seizure in the other, will help. Some paralytic cases of rabies may resemble Landry's paralysis.

In the lower animals there is a variety of diseases, such as dog distemper, dog hysteria, or brain tumour, which may simulate rabies. Then there is the *pseudo-rabies* or "mad itch" of Aujeszky. This virus is much more resistant to desiccation. Remlinger and Bailly found that the intraocular route is the most practical method of differentiation in experimental infections, because in *pseudo-rabies* the issue develops suddenly, which is not the case in true rabies. The infection is transmitted along the axis cylinders of the nerves, reaching the ganglia and segments of the cord, producing this degeneration which is probably responsible for the itching from which the disease takes its name. Pseudo-rabies has occasionally occurred in men, as a result of handling infected animals. It is a non-fatal disease and is characterized by intense itching.

Cases of "psychological" rabies have occurred in medical men and veterinarians bitten by dogs suspected of having rabies. Apart from psychological symptoms, there are no nervous changes.

TREATMENT

(a) Treatment of the developed disease.—No cure has yet been devised for the fully developed disease. As in other virus diseases, a potent antirabic serum has no effect once the symptoms have begun. Therefore, fully developed rabies in man must be treated on symptomatic grounds. Chloroform inhalations are given for control of painful spasms; chloral and bromides *per rectum* and, if possible, curare, subcutaneously. Morphia is apt to increase the mental excitement and suffering. Where the patient cannot swallow food, rectal alimentation is to be preferred to feeding by stomach-tube. Intubation or tracheotomy are probably both useless for the relief of dyspnœa and suffocation. Mechanical restraint is generally unnecessary and should not be resorted to except in violent maniacal forms. The attendants must preserve a calm and pleasant demeanour and, when speaking of the disease, should do all possible to reassure the patient.

(*b*) **Prophylatic treatment of person exposed to infection.**—Cauterization of the infected wound has been practised since time immemorial and, when properly carried out, it is undoubtedly of some benefit. It has been shown by experiment that the incubation period is prolonged, even when it does not prevent extension of the infection, and thus permits more time for establishment of immunity by antirabic inoculations. Actual cautery is very painful, and is efficient only if done thoroughly and instantaneously. The best method is to probe all parts of the wound with nitric acid. Carbolic acid is probably less effective.

(*c*) **Preventive inoculation.**—The Pasteur treatment for the prevention of rabies in exposed persons is designed to confer immunity during the period of incubation. The production of this immunity is necessarily a long process but, fortunately for humanity, the incubation period of rabies is normally much longer. In persons in whom, from a combination of factors, the incubation period is very short, the Pasteur treatment fails.

The principle upon which the Pasteur treatment is based rests upon the production of immunity by inoculation of modified rabies virus. This has been finally accomplished by serial passage of the virus through rabbits until a fixed degree of virulence has been reached, and secondly, by its attenuation by desiccation. The first of these processes is the more important and the one most frequently employed at the present time. The following methods have been employed:

(1) *Unmodified fixed virus*, introduced by Ferran: 0·08 grm. of cord of a rabbit dead of a fixed-virus infection is emulsified with the aid of fine sand, using 8 c.c. of salt solution or bouillon: 6 c.c. of the supernatant fluid is injected subcutaneously into three different parts of the body, 2 c.c. in each. The injections are repeated on five successive days.

(2) *The dilution of fresh-fixed virus*, a method introduced by Högyes, who maintained that attenuation could be more accurately controlled by diluting the fresh virus with salt solution and increasing the dosage, as treatment progressed, by increasing the strength of the emulsion. An improvement suggested by Harvey and McKendrick is to take smaller amounts of an original emulsion of fixed virus, prepared from the spinal cord of a rabbit dead of a fixed-virus infection, rubbing it up with sterile salt solution in the proportions of 1 in 100. Dilutions are prepared varying from 1 in 200 to 1 in 10,000. The dilutions are then used for immunizing. For severe cases, such as head or face wounds, as many as five injections are given daily in dilutions varying from 1 in 2,000 to 1 in 10,000, in the first four days, and subsequently, to the twentieth day, two or three times daily. Formulæ have to be devised to suit individual cases.

(3) *Fixed virus attenuated by drying.*—The original method of Pasteur, and one still most extensively practised, has the advantage that it may be administered by private practitioners at some distance from the laboratory, since dried virus can be preserved by glycerinization, and despatched in this condition. The original scheme of Pasteur has been greatly modified, according to the time consumed by

the treatment, by dispensing with some of the more attenuated cords, and by increasing or diminishing the dosage at individual injections. In the first four days two 3 c.c. injections are made daily of emulsions of cord dried *in vacuo* 14, 13, 12, 11, 10, 9, 8, 7 days respectively. The total course of treatment is twenty-one days.

(4) *Fixed virus attenuated by heat.*—A method advocated by Babes appears to be merely a more difficult method of attaining the same result as by the desiccation method.

(5) *Fixed virus acted on by glycerin.*—While glycerin possesses the power of conserving rabies virus in an active state for a month or more, on prolonged exposure this virulence is lost, although the immunizing power may be retained. This is the method which was advocated by Calmette, although rarely is this immunity sufficiently substantial to withstand subdermal inoculation tests with the fixed virus.

(6) Marie claimed that a rapid immunity is secured by treating a fixed virus partially neutralized by antirabic serum *in vitro*. It is said that a virus of high immunizing power, but of diminished infectious properties, can be administered. For this method one gramme of the medulla of rabbit is taken. A passage-fixed virus is rubbed up with 9 c.c. of veal broth and the emulsion strained through cloth. To 2 c.c. of this emulsion is added 4 c.c. of antirabic sheep serum, previously heated for thirty minutes at 56° C. The 6 c.c. of mixture is injected into the skin of the abdomen in two places and the same injections are repeated on three following days.

Formalinized virus which has been grown in tissue-culture can confer considerable immunity to mice, while after exposure to ultra-violet light it is still antigenic.

(7) The *carbolized fixed virus* is used at Kasauli and other stations in India. The whole brain is removed and a solution containing 1 per cent. of phenol in 0·85 per cent. salt solution is mixed and placed in a mortar in an incubator at 37° C. for twenty-four hours—sufficient to kill the virus. The suspension is stored at 0° C. while tests are being carried out, and is used as a vaccine after two to three weeks' storage.

Before inoculation the suspension is again diluted with an equal part of 0·85 per cent. salt solution, so that it finally contains 0·5 per cent. brain substance. Each patient, however severely bitten, receives 4 c.c. of this suspension daily for a period of fourteen days.

Serum therapy.—Although, when it was first discovered that rabies serum was capable of destroying rabies virus *in vitro*, hopes were entertained of its beneficent action in man, results have been disappointing.

The indications for the Pasteur treatment.—All persons who have been bitten by rabid animals, or who have had open wounds or scratches contaminated with the saliva of rabid animals, should receive the treatment. If, however, the suspected animal remains alive and *well* for ten days after the bite, treatment may safely be discontinued. In persons who have drunk the milk of infected cows, the possibility of infection is very remote, as gastric juice destroys the virus. Everyone who has been bitten by animals presenting symptoms of rabies should receive antirabic treatment, whether or not the suspicion is confirmed by histological examination, and pending the result of inoculation tests. Those persons who are bitten by animals which do not show any of the symptoms of rabies should not be exempt from the necessity for treatment until the biting animal, which should be carefully confined and watched, is shown to be free from the disease. It must be emphasized that histological examination is conclusive only when Negri bodies are demonstrable in the central nervous system.

The results of the Pasteur treatment.—Even with the most careful assessment of the results of treatment, it is extremely difficult to determine exactly the mortality-rate after the bite of a rabid dog. In untreated persons the estimated mortality is about 14·8 per cent. in 122 persons (Doebert, 1909). In 1935, 118,000 people received prophylactic inoculation. Figures published by the League of Nations show that from 1929–1935 only 0·4 per cent. of 524,258 people receiving antirabic treatment died from rabies. Though many were not bitten by rabid animals, nevertheless the impression remained that mortality would have been greater if they had not been so treated. As a general statement, it may be said that the total mortality of bitten persons subjected to antirabic inoculations is about 1 per cent., of whom half could not, on account of the short time permitted for the establishment of immunity, have been expected to live.

Immunization of animals.—In South America, cattle in many areas are being immunized prophylactically, while in certain towns dogs have been similarly treated. During the rabies outbreak in Singapore in 1937, arrangements were made to immunize the whole dog population, amounting to approximately 13,000. A killed virus should preferably be used for animal immunization.

Examination of suspected material for evidence of rabies.—The material generally consists of the head of some animal, most frequently the dog, and should be wrapped in cloths soaked in bichloride of mercury or other germicidal solutions, while for miscroscopic examination material may be sent already fixed in weak alcohol. For inoculation, the medulla which has been immersed in glycerin is suitable. Sections give better results than smears, but naturally take longer to prepare. If grossly contaminated with bacteria, the tissues should be treated with ether in a concentration of 10 per cent., which does not destroy the virus when allowed to act for two hours at 4° C.

In order to locate the hippocampus, or *cornu Ammonis*, the brain is placed upwards, with the temporal lobe lifted outwards from the median line until the cornu comes into view as a long cylindrical whitish body tapering at its anterior end. Smears are made on slides or cover glasses by crushing a small section of brain matter between two of them and drawing out under gentle pressure to produce a fairly thin film. After fixation they are stained in Unna's polychrome methylene blue for three minutes and examined after differentiation in 95 per cent. alcohol. Negri bodies stained in this way take on a magenta colour. In recent years it has been suggested that the mesencephalon, or oculomotor nucleus, is a more favourable site than the hippocampus. Morgan and McKinnon, however, found that in naturally infected dogs and donkeys, the hippocampus should be regarded as the site of election.

Another technical method is subdural inoculation, which is performed by a small trephine or jeweller's drill, to effect an opening into the skull large enough to admit a needle. The mouse is more suitable than the rabbit or the guinea-pig. Negri bodies can be demonstrated in mouse brains eight to nine days after inoculation (Sulkin and Nagle).

For the technique of removal of the spinal cord from rabid rabbits and the methods of drying *in vitro*, more authoritative works must be consulted. The present dry method consists of cutting 1 cm. pieces of cords of rabbits killed each day after inoculation, up to the eighth day. These should then be placed in glycerin in a cold place, where they will retain their potency for several weeks. Material conserved in this way can be distributed from the laboratory. It is first cut into half-centimetre pieces, each of which serves for one injection, when emulsified in 2½ c.c. of salt solution.

CHAPTER XX

DENGUE

Synonyms. Dandy Fever; Breakbone Fever; Chapenonada (Philippines); Sellar Fever.

Definition.—A specific fever conveyed by *Aëdes ægypti*, and, probably, other mosquitoes, occurring usually as a rapidly spreading epidemic. Throughout the febrile stages, and often subsequently, severe rheumatic-like pains are prominent. The disease in its active form lasts about a week, and is attended with little, if any, mortality. Severe cases may simulate yellow fever.

Geographical distribution.—Dengue has a wide distribution in the tropics and subtropics and is apt to occur in epidemics. It has appeared in Syria, Asia Minor, on the Ægean shores of Greece and Turkey, in North Queensland, in Charleston and Philadelphia in the United States, as far south as São Paulo in Brazil, and throughout Central and South America. It is endemic in the West Indies, and in Fiji, Samoa, and other Pacific islands. An extensive epidemic occurred in Greece; in Athens there were 239,000 cases up to September, 1928. Dengue is distributed along the whole African coastline on the west as far south as Loanda (Angola) and on the east to Durban. It is widely distributed in India, Ceylon, Burma, Malaya, Cochin China, Southern China, Dutch East Indies and the Philippines, Mauritius and other islands in the Indian Ocean. It occurred in the United States in 1922–23 and then not until 1934.

Epidemiology and endemiology.—The characteristic of dengue fever is its tendency to recur at intervals of years, sometimes in pandemic waves, during which, it may be, three-fourths of the population are attacked. The epidemic may last for one season or may be spread over several years. Between them, sporadic cases occur, by means of which the virus is maintained and forms the nidus of infection for a new epidemic but, owing to their mild nature, they are frequently not recognized. In pandemic form the disease often appears at a considerable distance beyond its usual confines, and may even ascend mountains to a height of 5,000 feet. The epidemiology appears to depend more upon conditions suited to the particular mosquito conveying the disease than upon those affecting man. Owing to the shortness of the immunity produced, control of dengue requires reduction of the mosquito index to zero.

When dengue spreads beyond its ordinary tropical limits, as for example in the epidemics of Philadelphia and Asia Minor, extension occurs only during the hottest part of the year—in the late summer and early autumn. Epidemics occur generally after the rainy season and, in the Pacific Islands, and in the southern hemisphere generally, the disease appears to have a seasonal incidence during June, July, and August.

It appears to prefer the coast-line, and the deltas and valleys of great rivers, to the interior of continents. The Grecian epidemic of 1928 was ascribed to the great increase of the population of Athens, and the establishment of a large non-immune community increased by a great influx of refugees. There were numerous breeding-places of mosquitoes in the

Piræus and it was estimated that 90 per cent. of the population became infected.

Ætiology.—Graham, in Beirut, Syria, first suggested that the disease was transmitted by a mosquito (*Culex fatigans*). Later, Ashburn and Craig (1907) demonstrated that dengue is caused by a filterable virus which is not contagious, and that a true immunity to re-infection is developed in certain individuals.

By a series of well-conceived experiments, Cleland, Bradley and MacDonald in Australia proved that the virus of dengue is conveyed by one species—*Aëdes ægypti* (formerly *Stegomyia fasciata*), but not by *Culex fatigans*. By subinoculation from one individual to another they transmitted the disease for four generations, and showed that the virus is present in the blood from the second to the fourth day. Subsequent experiments by Siler confirmed this work. He found that the blood in dengue is infective to the mosquito from eighteen hours *before* onset to the end of the third day of the illness. *A. ægypti* does not become infective for eleven to fourteen days, but then remains so for the rest of its life, but when the temperature is below 18° C. this does not occur. Passage of the virus through man to the mosquito fails either to attenuate or increase it. Simmons (1931) showed that *Aëdes albopictus* is probably the chief vector in the Philippines and probably also in Japan.[1] In Florida, it has been suggested on epidemiological grounds that *Aëdes tæniorhynchus* may also transmit dengue.

Blanc and Caminopetros studied the epidemiology of dengue in Greece and Macedonia, and showed that in these countries its distribution and that of *Aëdes ægypti* correspond, but in Australia the distribution of dengue is always rather less extensive than that of this species. An idea has been fostered that some affinity between the virus of dengue and that of yellow fever might exist, but this received no confirmation from the work of Stefanopoulo and others who subjected the sera of several individuals who had suffered from dengue to the yellow-fever mouse-protection test. Moreover, Dinger and Snijders fed mosquitoes (*Aëdes albopictus*) on dengue cases in Medan, Sumatra, and then dispatched them to Amsterdam, where they were re-fed on volunteers who subsequently developed dengue. It was thereby proved that the same virus in the same batch of mosquitoes reproduced different types of fever in different individuals. One might show the typical saddle-back temperature curve; another, continuous fever lasting seven days. From this they concluded that the five-day fever of Scheer and the seven-day of Rogers are not distinct diseases, as had been supposed.

Manoussakis has shown that the dengue virus can be transmitted almost indefinitely from one volunteer to another without alteration in virulence, and in each the incubation period was five to seven days. Twenty-five c.c. of blood was taken from a dengue case in the first twenty-four hours of the disease, placed in 200 c.c. of normal saline, sealed and placed in the incubator; after six days' incubation 6 c.c. of the supernatant fluid, injected subcutaneously into volunteers, gave rise to dengue. The virus can be dried and frozen without losing its virulence. This was shown by Hoffmann, Mertens and Snijders, who transported dried serum from

---

[1] Koizumi (1917) and colleagues claimed to have transmitted dengue by the bite of *Desvoidea obturbans*, a domestic mosquito, in Japan. In New Guinea *Aëdes scutellaris* (*see* p. 975) is the sole vector.

Java to Amsterdam and subsequently inoculated volunteers, reproducing typical fever 285 days after it had been abstracted.

The disease can be transmitted from man to various species of monkey: *Macaca mulatta, M. philippensis, M. funicatus.* In *M. mulatta* there is, as a rule, a leucopenia with reduction in the number of polymorphonuclear leucocytes. Though the virus is present in the blood the disease cannot be transmitted from monkey to monkey. Mice are not susceptible to inoculation. The so-called cattle dengue, sometimes termed three-day or ephemeral fever, though also due to a virus, has no relation to human dengue.

According to Pandit and Shortt, dengue virus has been cultivated in India on the chorio-allantoic membrane of the chick. By these means it was found that the virus persists in the blood for seven days. During convalescence immune bodies can also be demonstrated by this method.

Pathology.—On account of the low mortality, post-mortem records are few. In the autopsies recorded, localized pulmonary and intracranial inflammation and general lymphadenitis were the special features. Serous effusions in the neighbourhood of joints and inflammation of the crucial ligament of the knee have been noted, while myocarditis, nephritic lesions with degeneration of the cells of the convoluted tubules, and a specific encephalitis with leucocytic blocking of some of the cerebral capillaries, have also been recorded.

Symptoms.—The *incubation period* of the naturally acquired fever seems to be somewhat variable, generally from five to nine days, though sometimes it appears to be shorter. The course of the disease may be divided into three periods: stage of invasion, lasting two to three days; stage of remission, lasting twelve hours to three days; terminal fever and eruption.

Stage of invasion.—An attack of dengue may be preceded for a few hours by a feeling of malaise or, perhaps, by painful rheumatic-like twinges in a limb, toe, finger or joint, which, when confined to the knee-joint, are excruciating. Usually it sets in quite suddently. Sometimes the fever is ushered in by a feeling of chilliness or even by a smart rigor; sometimes a deep flushing of the face is the first sign. However introduced, the fever rapidly increases. The head and eyeballs ache excessively, and some particular limb or joint, or even the whole body, is racked with peculiar stiff, rheumatic-like pains, which, as the patient soon discovers, are much aggravated by movement. The loins are the seat of great discomfort, amounting in some cases to actual pain; the face—particularly the lower part of the forehead, round the eyes, and over the malar bones—may become suffused a deep purple; and often the skin over a part or the whole of the body, and all visible mucous surfaces, are more or less flushed. The mouth and throat are usually sore from congestion and perhaps from small superficial erosions. The eyes are usually much injected. This congested, hypersensitive and erythematous state of the skin constitutes the so-called prodromal eruption. There may be a *tache cérébrale.*

The cerebro-spinal fluid is under pressure; there is some increase in the albumin and a considerable increase in sugar, but no increase in the chlorides and no marked cellular reaction. This hypertension is probably the cause of the

severe headache, stiffness of neck, pain in the back and bradycardia which supervene in the stage of reaction.

These symptoms becoming in severe cases intensified, the patient, in a few hours, is completely prostrated. His pulse rises to 120 or more; his temperature to 103° F. (Chart 20), in some cases to 105°, even to 106 F°. He is unable to move owing to intense headache, severe pain in limbs and loins, and profound sense of febrile prostration. From time to time the skin may be moistened by an abortive perspiration, but for the most part it is hot and dry. Gastric oppression is apt to be urgent, and vomiting may occur. Gradually the tongue acquires a moist, creamy fur, which, as the fever progresses, tends to become dry and yellow. In this condition the patient may continue for from one to three or four days, the fever declining somewhat after the first day.

In a proportion of cases, and particularly in certain epidemics, crisis does not occur, the fever slowly declining during a period of three or four days. In some epidemics enlargement of the lymph glands, particularly of the cervical group, has been noted, especially by Helser (1937), and more recently by Findlay and Brookfield (1943) in Nigeria. In one epidemic in St. Thomas in the Virgin Islands adenitis was recorded in 62·5 per cent.

Stage of remission.—When the second stage is established and the thermometer has sunk to normal, the patient is sufficiently well to leave his bed and even to attend to business. The tongue clears, and the appetite and sense of well-being return to some extent.

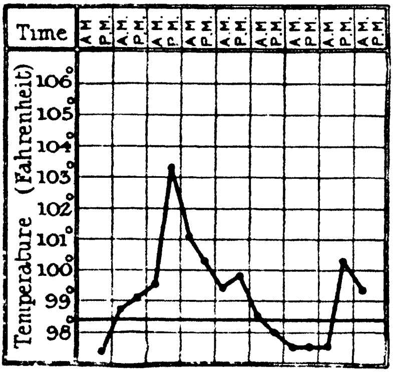


Chart 20.—Dengue. (*After Cleland and Bradley.*)

Terminal fever and eruption.—The state of comparatively good health continues to the fourth, fifth, sixth or even to the seventh day, counting from the onset. Then there is generally a return of fever, slight in most cases, more severe in others. With the recurrence of the fever a rubeolar eruption, consisting of dark, dusky spots, appears. The pains likewise return, perhaps in more than their original severity. Though the fever subsides in a few hours, the eruption, at times very evanescent, may be apparent for two or three days longer, to be followed very frequently by an imperfect furfuraceous desquamation.

Characters of the eruption.—The terminal rash of dengue possesses very definite characters. It is absent in a very few cases, but in many, being slight, it is overlooked. Usually it commences on the palms and backs of the hands, extending for a short distance up the forearms. It quickly extends, and is best seen on the back, chest, upper arms (Plate VII, Fig. 2), and thighs. Here it appears at first as isolated, slightly elevated, circular, reddish-brown, rubeoloid spots, ⅛ to ¼ in. in diameter, thickly scattered over the surface, each being isolated and surrounded by sound skin. There may be a general coalescence, isolating here and there patches of sound skin ; in this case the islands of sound skin give rise, at first sight, to the impression that they constitute the rash—a pale eruption, as it were, on a scarlet ground, giving an appearance " midway between scarlet fever and measles." The spots disappear on pressure, and never, or rarely, become petechial. Usually the face escapes. They fade in the order in which they appear—first on the wrist and hands ; then on the thighs and body ; lastly, on the legs and feet, but they may still be visible three weeks after recovery from fever. Desquamation may persist for two or three weeks. In many it is trifling ; for the most part it is furfuraceous.

At this stage the characteristic slowing of the pulse, which may fall as low as 44 per minute, and leucopenia, which may reach 1,200 leucocytes, are noted ; the latter is mostly due to a marked decrease of the polymorphonuclear cells, which may be reduced to 40 per cent., and to a relative increase of the lymphocytes (up to 53 per cent.).

Rheumatoid pains persist for some time after convalescence has been established. They are usually worse on getting out of bed and on moving the affected part after it has been at rest for some time, and are somewhat relieved by rest and warmth. In some cases a periarthritis of the knee- or ankle-joint supervenes and may cause considerable disablement, which does not clear up for months or years. Dengue pains persist in the small muscles of the hands and soles of the feet, probably located to the deep fascia. They eventually wear off. Complications are few. Albuminuria, parotitis, orchitis, herpes labialis and epistaxis have been recorded.

Convalescence may be much delayed by anorexia, general debility, mental depression, sleeplessness, evanescent feverish attacks, boils and urticarial, lichenoid and papular eruptions.

In Europeans an attack of dengue very often leads to a condition of debility, necessitating temporary change of climate, or even return to Europe.

Variability of epidemic type.[1]—Judging from the published descriptions, there is considerable variety in the symptoms of this disease in different places and in different epidemics. Some authors mention swelling and redness of one or more joints as a common and prominent symptom ; others refer to metastases of the pains, enlargement of submaxillary glands, general adenitis, mental depression, hæmorrhages, and so forth. However this may be, the essential symptoms in well-marked cases are the same practically everywhere and in all epidemics, viz., suddenness of the rise of temperature, an initial stage of skin congestion, limb and joint pains, and a terminal rubeoloid eruption. In a sudden outbreak in New Caledonia Mayrac recognized the following types :

(1) a simple febrile type with an urticarial rash ;
(2) nervous type with intensive headache ;
(3) gastro-intestinal type ;
(4) a type in which joint pains were the main feature.

---

[1] Several investigators, notably Findlay and Brookfield, think that these are varieties of the dengue virus, but there is very little evidence to support this suggestion. *Fièvre rouge* of the Congo is also probably dengue. Jack (1937) upon observations in 1,000 cases at Razmak and in N. India described " sellar fever " with dengue-like symptoms, but an absence of marked rash. There was no possibility of mosquito transmission in these localities.

In the Athens epidemic, some of the following clinical manifestations were noted: gastro-intestinal disturbance, vomiting, epigastric pain, hiccough, hæmorrhage into skin and mucosa, and complications such as parotitis, otitis, furunculosis and broncho-pneumonia. In some acute cases with early and severe gastro-intestinal phenomena, bleeding from the gums and hæmatemesis were seen. Encephalitic symptoms have also been described. The spleen and liver are not enlarged.

Relapses are not uncommon in dengue, and second and even third attacks during the same epidemic have been recorded. As a rule, however, susceptibility is exhausted by one attack.

Immunity.—Schule pointed out that certain of his volunteer American soldiers proved remarkably resistant to experimental inoculation with the dengue virus, and these were individuals who had been resident for some time in an epidemic area of the disease. Probably, immunity is due to previous mild attacks. The immunity in dengue does not last more than six months ; it thus differs from that of yellow fever, which is life-long.

Mortality.—In uncomplicated dengue the mortality may be said to be almost nil (0·1 per cent., Hare). During the 1928 epidemic in Greece Cardanutis gave the mortality-rate as 1 in 61,000.

Diagnosis.—Dengue must not be confounded with yellow fever, Rift Valley fever, rötheln, scarlatina, measles, syphilitic roseola, influenza, cerebro-spinal meningitis, typhus, hæmorrhagic smallpox, enteric, phlebotomus fever, seven-day fever (leptospirosis), rheumatic or malarial fever. A knowledge of the distinctive features of these diseases, and the fact that dengue is attended with a rash and with articular pains, and that it occurs in great and rapidly spreading epidemics, should prevent any serious error.

Treatment.—Were it possible to secure perfect isolation and immunity from mosquito-bite for the individual during an epidemic of dengue, doubtless he would escape the disease. Even comparative isolation is attended with diminished liability.

Like the allied fevers, dengue runs a definite course ; therefore it is useless to attempt to cut it short. The patient should go to bed as soon as he feels ill, and should keep his room until the terminal eruption has quite disappeared and he feels well again. Ten days is not too long to allow in severe attacks. As in influenza, light liquid diet, rest, and the avoidance of chill conduce powerfully to a speedy and sound convalescence. At the outset of the fever some saline diaphoretic mixture, with aconite, may be prescribed with advantage. If the pains be severe and the fever high, antipyrin, phenacetin, belladonna, or vinum colchici (15 min. t.d.s.) give great relief. Cold applications to the head are comforting. If the temperature rises to 105° F. or over, cold sponging or the cold bath ought to be used. If the pains continue very distressing, a hypodermic injection of a minute dose ($\frac{1}{10}$gr.) of morphia will afford welcome relief and do no harm. Purgatives and emetics should be avoided unless pronounced constipation, or a history of surfeit, urgently demands their exhibition. The pain caused by the muscular movements entailed by purgatives more than counterbalances any advantage. In the Athens outbreak, urotropine in full doses was given in the early stages and, if pains were severe, aspirin, pyramidon and caffeine. For cerebral symptoms, which in some patients might be an important feature, bromides and strophanthus are indicated. Alcohol in the early stage is not advisable. Freshly-made lemonade, or iced water, will be acceptable during the fever.

For the pains experienced during convalescence, rubbing with opium or belladonna liniment, gentle massage, electricity, salicylates, and small doses of iodide of potassium have been advocated. Debility or anorexia indicate tonics, such as quinine, strychnine, mineral acids or vegetable bitters and change of air.

Prophylaxis is the same as for yellow fever and for other mosquito-borne diseases, and is directed against infected mosquitoes.

Prophylactic inoculation.—St. John and Holt attempted to produce a dengue vaccine. Vaccine made from the liver and spleen of dengue-infected monkeys did not protect volunteers from an attack; but there was evidence that the disease was mitigated in the inoculated.

CHAPTER XXI

PHLEBOTOMUS FEVER

Synonyms. Papataci Fever; Three-day Fever; Sandfly Fever, "Dog Disease," "Hundfieber."

Definition.—A specific fever of short duration and no mortality caused by a virus introduced by the bite of a sandfly (*Phlebotomus*).

History.—This disease has been recognized clinically for upwards of a century, and described under a variety of local names; but its definite relation to its transmitting agent, although suspected by McCarrison in Chitral in 1903, was not established until 1908, when Doerr published his observations, since confirmed by Kilroy, on the infectivity of the blood in this form of fever and the rôle of the sandfly as transmitter. Whittingham described the various stages in the life-history of the phlebotomus, and succeeded in rearing these insects in captivity.

Geographical and seasonal distribution.—The range of phlebotomus fever is probably co-extensive with that of the insect transmitter. In the tropics it may break out at any time as an epidemic amongst new arrivals; in the subtropics it occurs only or principally during the summer and early autumn, though in Palestine and Syria spring and autumn outbreaks occur. Natives of the endemic area appear to be immune. Where the phlebotomus is absent, e.g. Bermuda, this fever is not found. In some phlebotomus-haunted places as many as 75 per cent. of new-comers are attacked. This fever was much in evidence during the 1914–1918 war in Gallipoli, Salonika, the Ægean Islands, Egypt, Palestine, Syria, Iraq, and India, but there is no record of it among troops in East Africa. Widely distributed in Africa and Asia, sandfly fever is found in the Caucasus, Chitral, and the Himalayas, up to a height of 4,000 feet. In the New World it has recently been found in Northern Argentina and in Northern Brazil.

Ætiology.—The virus resides in the patient's blood during the first two days of the fever. It is ultramicroscopic, passing through filters which arrest *Brucella melitensis*. According to Doerr, the virus may be transmitted hereditarily through the egg and larva of phlebotomus to the imago, but this has not been firmly established. A short sharp fever has been produced in monkeys after intravenous injection of sandfly-fever blood. In Egypt, it is said, a similar fever exists in cattle, but it is doubtful whether this, also called cattle dengue, has any relation to sandfly fever. Little is yet known of the physical properties of the virus. According to Whittingham, it may survive the winter, either free in the soil or within the bodies of phlebotomus larvæ which inhabit such sites as moist soil and porous walls. The larva is thought to extract the virus in feeding upon the fæces of the adult fly; but Moshkovsky and his colleagues in Moscow showed that it may be transmitted by the female phlebotomus to the egg and so to the larva. This is the only instance in which an animal virus has been transmitted hereditarily by an insect vector, but may be an important epidemiological consideration and may explain the suddenness and extent of outbreaks of sandfly-fever on the Indian frontier in the spring. In one case, infection followed the bites of recently hatched female sandflies, thus disproving the supposition that the virus is transmitted only after the sandfly has already digested a meal of blood.

Shortt, Poole and Stephens showed that, as with dengue, the sandfly-fever virus can pass through L_3 and L_5 Chamberland filters, and that it is present in the highest concentration in the blood during the first and second day of the disease. They proved that it can survive outside the body for sixty hours. Shortt, Pandit, Anderson and Rao cultured the virus on the chorio-allantoic membrane of the chick embryo; by subsequent inoculation it could be demonstrated in monkeys for an average of 11 days, and subsequently immune bodies up to 69 days. According to Russian workers (Demina) the virus causes a proliferation necrosis of the chorio-allantois. It can be inactivated by treatment with commercial formalin, 1 in 1000, and it can be dried and preserved in a vacuum desiccator for eight months.

In cases of fever and in convalescents the presence of the virus in the blood can be demonstrated by egg-culture up to three or four weeks from the onset of fever.

Representatives of the genus *Phlebotomus* are to be found in most tropical and subtropical countries. The various species are usually designated "sandflies." They are exceedingly minute, very delicate, greyish, or brownish, somewhat slenderly-built insects that bite principally during the night and that can pass easily through the meshes of an ordinary mosquito-net. The powers of flight are feeble; more usually the insects progress by a series of short skips.

P. papatasii, the species on which Doerr's observations were made (hence one of the names for the disease, papataci fever), lays about forty eggs, selecting for the purpose damp localities such as the walls of cellars, of latrines, cesspools, crevices in walls, caves, and embankments. The cycle of egg, larva and imago takes about one month in warm and upwards of two months in cooler weather (*see* pp. 951–952). It has not been determined which of the many species of phlebotomus, other than *P. papatasii*, conveys this fever. The insect can transmit the infection after an incubation period of six days.

Pathology.—Dengue and phlebotomus fever have several important points in common, a circumstance suggesting the possibility of a common or, at all events, a similar origin. Each is transmitted by an insect; the viruses occur in the blood-stream and are filterable; they are diseases of warm climates only; and clinically, they are characterized by a short incubation period and a brief and rapidly developed fever which is usually associated with relatively slow pulse and leucopenia, and relative decrease of the polynuclears. There is no evidence that these diseases are mutually protective. The post-mortem appearances of sandfly fever are unknown.

Symptoms.—The bites of the sandfly occasion a considerable amount of irritation, resulting in hyperæmia and even in œdema. After an incubation period of from four to seven days, with or without a prodromal stage, the fever is ushered in suddenly by slight or more severe rigor, and may reach 105° F. The face becomes flushed and swollen, frontal headache is intense, and there is usually severe general aching and stiffness in the back of the neck. Pain at the back of the eyes, accentuated by pressure on the globes or by the least movement of the head, is characteristic. Supraorbital headache is also quite common. There are influenzal pains in the back and legs and general stiffness of the muscles. More rarely the pain is referred to the epigastrium. A sense of band-like constriction round the lower part of the thorax is sometimes so prominent as to resemble epidemic pleurodynia, or Bornholm disease. The patient is drowsy, but suffers from insomnia. The conjunctivæ are so injected that the eyes have been compared to those of a mastiff. The tongue has a central fur. The fauces and palate are often congested, and are studded with small vesicles ; it has been remarked that they are devoid of any surrounding mucosal inflammation. The vesicles are not strictly peculiar to sandfly fever as they have also been noted in infective hepatitis. In from twenty-four to thirty-six hours the temperature has reached 103–104° F. (Chart 21). It keeps about this point for a day longer, and then begins to fall, with or without epistaxis, vomiting, sweating and diarrhœa, reaching the normal about the end of the third or beginning of the fourth day. The patient continues debilitated, especially mentally, for a week or two longer. According to Lambert, the name " three-day fever," applied to the disease, is misleading, since the pyrexial period may occasionally vary from two to eight days. In some cases there are several days of apyrexia followed by a secondary rise of temperature lasting a day or two.

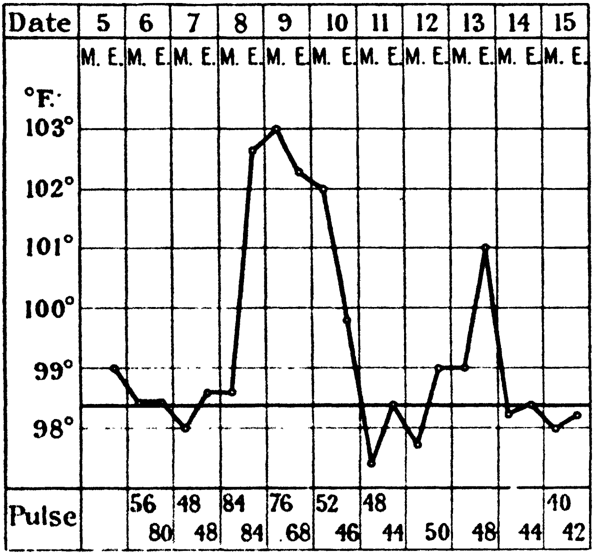


Chart 21.—Phlebotomus fever showing prodromal period, typical attack, recrudescence and bradycardia. (*Lambert, Jl. Roy. Nav. Med. Ser.*)

The blood-picture shows a slight leucopenia, without serious alteration in the proportion of mononuclears, especially from the second to fourth day, after which there is a leucocytosis of 15,000–20,000. The pulse-rate is relatively slow. Relative bradycardia is noticeable by the second day of the disease, as soon as the patient complains of headache, and is possibly due to increased pressure of the cerebro-spinal fluid. An absolute bradycardia is noted at the end of the fever.

Le Gac and Albrand first recorded that the cerebro-spinal fluid is under increased pressure and shows from 10 to 110 lymphocytes per cu.mm. Albumin is always increased and the chlorides slightly decreased. These findings have been amply confirmed.

Shee (1942) described varying degrees of choking of the optic disc, ranging from blurring of the edges to papillœdema. This was seen in the early stages, but in severe cases was visible at the crisis.

No serious complications occur, but in some years diarrhœa, in others pharyngitis, are features of the disease. Constipation, vomiting and stiffness of the muscles at the back of the neck are not uncommon. Second attacks are by no means rare, but are milder, and third and fourth attacks have been recorded. Shortt proved that immunity may sometimes persist for one year after an attack. On the whole, children suffer less severely than adults.

Pearson (1941) drew attention to the similarity of benign lymphocytic meningitis and sandfly fever. There seemed to be in Palestine some connection between the incidence curve of the two. The cardinal signs of sandfly fever—frontal headache, orbital pain, photophobia, pains in the back, fever and conjunctival congestion—are duplicated in benign lymphocytic meningitis. The debility which ensues in some individuals is quite out of proportion to the intensity and duration of the initial attack. Acute synovitis as a complication has been observed in Iraq during the present war. The mortality is nil.

Attention has quite recently been drawn to a dermatitis, known as " Harara " (*i.e.* heat), which is common in Anatolia, Syria and Palestine during the sandfly season, and is a reaction due to their bites.

Diagnosis.—It is extremely difficult in the early stages to distinguish this fever on clinical grounds from malaria (especially subtertian), from paratyphoid, dengue, typhus and influenza. In typhus the greater hebetude, and in influenza the respiratory catarrh, must be taken into consideration.

Treatment.—The most valuable drug in the treatment of sandfly fever is opium ; 30 drops of the liquor opii sedativus may be given at the onset. It greatly relieves the headache. Quinine is useless. Tincture of iodine should be applied to the bite. The headache has been relieved by lumbar puncture. Whenever possible, patients should be nursed under sandfly nets.

Prophylaxis.—As phlebotomus fever appears to be a disease of locality, houses and places believed to be infected should be avoided and, where possible, disinfected.

To diminish the local sandfly pest, all rubbish should be burned or otherwise got rid of, ruinous walls demolished, cracks in walls filled in with tar or mortar, latrines smoked with sulphur fumes and put into sanitary condition, and dark damp places dried, whitewashed, and ventilated. No gardens or cultivated ground should be permitted in the immediate vicinity of buildings. Creepers should not be allowed to grow on barrack walls. Benzene polychlorines, widely used in agriculture, are useful for destruction of sandfly larvæ, and are applied in solution in the strength of 75 c.c. to every square metre. The adult flies can be killed in numbers by " swatting." By these and similar measures much can be done to control the infection. Unfortunately, a net having a mesh sufficiently small (i.e., 45 holes to the inch) to keep out sandflies is intolerable to a white man in a hot climate. As the phlebotomus does not fly higher than 10 ft., removal to an upper story is a very effectual preventive measure. *Flytox* and *Flit* are the best sprays for destroying adult sandflies. Special staffs are necessary for the daily destruction of these insects in dwellings. Special apparatus is used and a flush of fluid is directed against the sandflies sitting on the walls or in corners. In hospitals in an endemic area every ward and annexe, including latrines, should be treated with Flit three times daily.

Repellents, as in malaria, have been employed, especially methyl phthalate.

Choyce recommended, as a general prophylactic measure, 5 per cent. thymol made up with firm wax into a candle and rubbed into the skin, where it forms an oleaginous covering.

To reduce the incidence of sandfly-bites general measures should be instituted. Shorts should not be worn after sundown, wrists and ankles should be smeared either with thymol ointment, or with " vermijelli," or oil of citronella. Wellington boots afford a good protection to legs and ankles after dusk. During the present war in the Middle East, it has been found that blackout conditions increase the liability to sandfly-bites, because men prefer to sit outside, rather than in tents or huts.

Air-currents have a marked effect on sandflies, and Whittingham showed that the most effective way of ridding quarters of these pests is to create a strong current by electric fans.

Shortt and his colleagues used the cultural virus as a vaccine. In inoculated volunteers immune bodies in the serum were subsequently demonstrated.

CHAPTER XXII

THE POCK DISEASES

At the present time classical smallpox is largely restricted to tropical and subtropical countries, where the preventive measures responsible for the decline of this disease in temperate climates are more difficult to enforce. In British India, for example, the number of cases of variola reported during the year 1938 was 82,640, with a mortality of 27 per cent. During the same period there were severe outbreaks in China (Hong Kong and Shanghai) and in Nigeria ; and a mild form of the disease with no fatalities was prevalent in the southern states of the United States.

During the last few years much has been learnt about the nature and properties of the causal agents of the pock diseases. The greater part of this work has been carried out with vaccinia, and it is therefore necessary to define at the outset the relationship between this virus and variola. That smallpox and all the animal pock diseases are closely related is certain. Vaccinia may be regarded as the virus in its original form from which the more complex viruses, including human variola, have evolved and to which they revert when passed through the cow or calf. Variola virus has also been converted into an attenuated form by inoculating human infective material into monkeys and then inoculating filtrates obtained from the monkey lesions intratesticularly into rabbits. After a number of passages in the rabbit testis the virus is able to produce a confluent eruption when rubbed into the freshly-shaved skin of these animals. This strain of virus is indistinguishable from the classical strains of vaccinia which were obtained by passage of human smallpox through calves or naturally occurring cowpox. The transition from variola to vaccinia is, fortunately, not reversible, so that once a strain of virus has been adapted to the calf or sheep it can be inoculated into man, producing in him a mild illness which renders him subsequently immune to the virulent form—smallpox. On rare occasions vaccination gives rise to a generalized papular or vesicular eruption with severe constitutional symptoms which may terminate fatally. This condition is believed to be due to an abnormal susceptibility to vaccinia, and not to an increase in virulence of the virus.

Nature and properties of the causal agent.—The infective agent of vaccinia is a spherical body, measuring about 0·17 μ in diameter, to which the noncommittal term " elementary body " is applied pending the settlement by further research of the much-disputed question whether viruses should be regarded as micro-organisms or macro-molecules. These bodies were first seen and described in 1887 by Dr. John Buist of Edinburgh, who found them in the vesicle fluid of smallpox and vaccinia. In 1906 they were rediscovered by Paschen and are frequently referred to as " Paschen bodies." It is only during the last few years, however, that the bodies have been proved to be the causal agents. Methods have now been evolved of preparing pure suspensions of the elementary bodies from the skin lesions produced in rabbits and sheep by specially-selected strains of vaccinia virus. These pure suspensions have been employed in recent studies of the physical, chemical and biological properties of the virus, and they are also being used experimentally in place of crude lymph for prophylactic immunization against smallpox. Chemical analysis has shown that the elementary body is composed mainly of nucleo-protein together with a carbohydrate and a lipoid fraction. Highly-purified suspensions of the elementary bodies contain phosphatase and catalase, and these enzymes are believed to be inherent in the virus; no dehydrogenase activity has been demonstrated. Sedimentation photographs of elementary body suspensions, obtained with the Svedberg centrifuge, show fairly well-defined boundaries, indicating that the variation in size of the particles is very small. The bodies have an unusually high charge and electrophoretic mobility; they are also exceptionally sensitive to flocculation by salts. Although their size is below the limit of optical resolution for visible light, they can readily be seen with the dark-ground microscope.

When inoculated by inunction into the skin, the elementary bodies penetrate the cytoplasm of the epidermal cells and there proceed to increase in number, thus producing, perhaps with the addition of material derived from the infected cell, the so-called acidophil inclusion body which was described long ago by Guarnieri. The virus within the cells causes them to increase in size and also to proliferate freely. This increase in thickness of the epidermis, together with œdema and hyperæmia of the subjacent dermis, is responsible for the papule. Later, the cells forming the centre of the papule degenerate and liquefy, thus producing the characteristic vesicle, in the fluid contents of which the elementary bodies are found in enormous numbers. The vesicle is rapidly converted into a pustule by the immigration of inflammatory cells, mainly polymorphonuclears, derived from the dermis. The fluid provides an excellent culture medium for staphylococci and other organisms, and the leucoyctic response is largely due to this secondary infection. In non-fatal cases the crusts or scabs, which separate after the pustule has dried, contain active virus. The high infectivity of smallpox, however, is probably not due to dissemination of the crusts but to lesions present in the mouth, throat and lungs. The expired air of patients suffering from variola has been shown experimentally to contain elementary bodies. The air in the vicinity of the patient thus becomes charged with microscopic droplets of water which he has exhaled. These droplets evaporate, leaving the elementary bodies suspended in the air where, being so minute, they may remain for long periods. A susceptible person breathing such contaminated air becomes readily infected. Contact with fomites is undoubtedly responsible for some infections, but the epidemiological characters of the disease can only be fully explained by the assumption that the virus is air-borne.

Vaccinia and variola, in common with other viruses, cannot be cultivated in the absence of living susceptible cells. The virus can be grown readily in tissue cultures of rabbit testis or corneal epithelium, and proliferation also takes place in a fluid medium consisting of rabbit serum and Tyrode's solution to which small amounts of minced rabbit kidney or testis have been added. Vaccinia also grows without difficulty when implanted on the chorio-allantoic membrane of the developing chick embryo. Both these methods have been used successfully to procure a supply of bacteria-free virus material for prophylactic immunization. This culture virus may be inoculated by scarification in the usual way, or it may be injected intracutaneously. The latter method has the advantage of leaving no scar, but since a vaccination scar is the one infallible sign that a person has been immunized against smallpox, it would increase the difficulties of controlling an epidemic, especially among coloured races. There is evidence that strains which have been grown *in vitro*, or on the egg membrane for a long time, become attenuated so that they may fail to induce a good immunity when inoculated into man. Generalized vaccinia has been known to occur as the result of vaccination with virus grown on the chick embryo.

Laboratory diagnosis.—Elementary bodies can readily be demonstratedin the vesicle fluid by the dark-ground microscope. *The technique is the same as that for the detection of spirochætes. Permanent preparations are best prepared by using Gutstein's method :

Solutions needed.—(*a*) 1 per cent. methyl violet in distilled water.
(*b*) 2 per cent. $NaHCO_3$.

Technique.—A drop of the vesicle fluid is spread on a perfectly clean microscopic slide as for a blood film. Films are dried in the air, or in an incubator, and rinsed in physiological saline and then with distilled water. When dried, the film is fixed in methyl alcohol (or ethyl alcohol) for half an hour or more and the slide put in a dry Petri dish. Equal parts of solutions (*a*) and (*b*) are mixed in a test tube, filtered at once on to a slide, covered with a lid and incubated at 37° C. for twenty to thirty minutes. Rinsed in distilled water, they are dried and mounted in cedarwood oil or liquid paraffin. The elementary bodies are stained distinctly and intensely a light violet colour.

Finding elementary bodies in the vesicle fluid is of no value in differentiating smallpox from varicella since the infective agent of the latter disease also takes the form of elementary bodies and the two viruses are indistinguishable under the microscope.

The best-known method for the serological diagnosis of smallpox is that of Gordon, Craigie and Tulloch. The pocks are lightly scraped with a scalpel and the material so obtained is suspended in saline. The suspension is clarified by light centrifugation and then mixed with a series of dilutions of rabbit anti-vaccinial serum. The tubes are incubated at 87° C. A positive reaction is marked by the appearance of a finely-floccular precipitate. The reaction is specific for variola and vaccinia ; it is probably a mixed precipitation and agglutination. Diagnosis may also be made by the complement-fixation test, using a suspension of the crusts as antigen.

The serum of a patient who is recovering from an attack of smallpox contains agglutinins which react specifically with variola elementary bodies. These antibodies are not present in detectable amounts until the second week of the disease, and the reaction is therefore of little diagnostic value.

Serological methods have so far failed to discover any antigenic difference between variola major and variola minor. It is thus evident that the diagnosis of smallpox must be made mainly by clinical methods but that laboratory tests may be of use in doubtful cases.

* Van Rooyen and Illingworth (1944) confirmed Paschen's observation that the elementary bodies of [illegible] a those of varicella, and are easily demonstrated in the papular and vesicular stages. [illegible]

A Note on the Treatment of Variola

The mortality from smallpox, excluding the severe toxic and hæmorrhagic forms of the disease, is largely due to secondary pyogenic infection of the respiratory tract. Energetic measures to combat this secondary infection should be commenced at an early stage. The sulphonamides are highly-effective chemotherapeutic agents against streptococcal infections, and this form of treatment has proved of great value in smallpox. The use of sulphonamides, however, is not without danger on account of their toxic properties, and administration to patients who are already seriously ill would have to be undertaken with caution. Clinical reports on the value of the drugs in the treatment of smallpox are, in a limited number of cases, favourable. Drug treatment should possibly be combined with the injection of large doses of concentrated multivalent antistreptococcal serum.

The treatment of smallpox by potent antivaccinial serum has as yet not received the attention which it appears to deserve. Such treatment would need to be given early, since the secondary fever and its attendant dangers would obviously not be influenced by it. Antivaccinial serum of high potency can be prepared by immunization of the horse, and it can be concentrated by the usual methods of serum-protein fractionation.

ALASTRIM

Synonyms.—Amaas; Kaffir milkpox; West Indian modified smallpox; parasmallpox; variola minor.

Definition.—This disease has been noted by many writers in the West Indies and South Africa.

The name is derived from the Spanish *alaster*, meaning to scatter or strew over (referring to the distribution of the rash). It is a disease of little or no mortality, and resembles smallpox in its mitigated form. Indeed, the individual case of this disease is clinically identical with a mild case of smallpox; they can only be distinguished one from the other in the mass.

Geographical distribution.—The disease has been recorded from the West Indies, South and Central America (especially Brazil), Africa, the Mediterranean area, and during the last 30 years from time to time in Great Britain. The most noteworthy epidemic was in Trinidad in 1902.

Epidemiology.—A striking difference between classical smallpox and alastrim is seen in the rate of progress through an unvaccinated community. Smallpox becomes rapidly epidemic, whereas alastrim can only be said to "smoulder," alternately waxing and waning, but never attaining really epidemic proportions. This, no doubt, depends upon the infectivity of the two viruses. There appears to be no seasonal incidence.

The spread of alastrim is brought about by intimate contact and overcrowding.

Ætiology.—Alastrim is very infectious to man, and attacks both sexes: no racial immunity has been observed. The causative organism has not been discovered, though Guarnieri bodies have been described from the lesions (*see* p. 379). The virus is infective under experimental conditions for monkeys and calves, and produces lesions when inoculated into the cornea of rabbits. The crusts off the pocks are believed to convey the virus of the disease. The infectious agent probably resides in the nasal and buccal secretions at an early stage. Vaccination protects against alastrim in a very high degree. This, and the fact that two attacks may occur in the same individual, are common both to alastrim and to smallpox.

Pathology.—The lesions are present on the buccal mucous membrane as well as on the skin, and may extend from the palate down the trachea into the bronchi. The actual pocks appear to involve the skin tissues to a degree intermediate between those of chickenpox and smallpox; they rarely leave any scarring.

Symptoms.—The *incubation period* averages about fourteen days; prodromal symptoms may or may not be present. When observed, they are those of an influenza headache, with generalized aches and pains. Severe headache, vomiting, and rigors, typical of the onset of smallpox, are rarely noted. The eruption commences usually on the third or fourth day, but in some cases there is a complete intermission of all symptoms, during which the patient may return to his duties under the impression that he has recovered from an attack of influenza; after the lapse of the quiescent period the eruption appears first on the face and palate, then on the hands and arms, and later on the lower extremities. Thus, in these cases there is a prodromal period of seven or eight days.

Individual lesions.—The papules can be palpated under the skin even before they are visible. As a rule, the eruption appears in one crop, and closely resembles that of smallpox in every respect, any differences being due to the more superficial situation of the pathological process in the skin. The pock may be umbilicated, but collapses more completely on being punctured than does the smallpox pustule, that is to say, it is less definitely multilocular. Drying or crusting begins at about the end of the first week, and crusts have usually fallen by the end of the second or third, at which period the patient is considered to be free from infection.

The rash naturally differs somewhat in appearance on a dark skin; the individual pustules, when ripe and full of pus, show as light creamy-coloured areas, in contrast to the dark purple of the surrounding inflammatory zone, and appear like pearls upon a dark background.

Distribution of the eruption.—This is identical with the distribution of the smallpox eruption, which is centrifugal, and it serves to distinguish alastrim from chickenpox, the rash of which has a centripetal distribution. As in smallpox, the most protected parts of the skin are most free from eruptions, i.e. axillæ, groins, and abdomen. The parts most affected are the face, scalp, shoulder, back, arms and legs. Any part which has been previously specially exposed to irritation is more profusely affected; thus, pocks are apt to cluster at the site of old burns or scars.

Confluent rashes may occur but, though the appearance of the patient is somewhat alarming, his general health appears to be but little disturbed. These cases may be associated with a considerable fever.

It has been noted by most writers on this subject that the fetor accompanying the rash of true smallpox is not present in alastrim.

Prodromal rashes are absent.

The mortality-rate is minimal; in the series recorded it is about 0·45 per cent. (Ribas and Moody).

Treatment is symptomatic only ; patients should be isolated in a smallpox hospital or elsewhere.

Prophylaxis.—Vaccination offers the most efficient method of protection against this disease, as in smallpox. In spite of the mildness of alastrim, it is considered desirable at present to treat it as a form of smallpox, and not only to isolate patients but to vaccinate contacts.

Subsection F—FEVERS DUE TO ATMOSPHERIC CAUSES

CHAPTER XXIII

HEAT-STROKE, HEAT EXHAUSTION AND SUN-STROKE

Preliminary.—Leonard Hill states that in hard muscular work the heat production is great and, even when well trained, a man does not turn more than one-third of the energy generated into work, two-thirds being converted into heat. An ill-trained man, on the other hand, has an efficiency no higher than a steam-engine, and converts 10-15 per cent. of food energy into mechanical work and wastes the remainder in the form of heat. Sweat cools the body by evaporation ; the latent heat of evaporation in the chief factor concerned.

Jones and Mankin, in their studies on submarine ventilation in tropical waters, found that during long submerged runs with high atmospheric temperatures and a high relative humidity, those men who were near electric fans suffered no discomfort, whilst those who were some distance away were distinctly uncomfortable, showing the beneficial effect of removing the envelope of moist warm air from the body and aiding evaporation.

C. J. Martin, in his work on heat regulation in man, found that the mechanism is essentially an "adjustable insulation." A comfortably clothed individual, sitting in a room at 15° C. at 50 per cent. of relative humidity, loses 44 per cent. of excessive heat by radiation, 31 per cent. by convection, and 20 per cent. by evaporation of moisture from the lungs and skin. A resting man produces some 1·2 large calories of heat per minute, which, if lost by evaporation of moisture, must entail a loss from the body of at least 2 c.c. of water per minute. Strenuous work necessitates the evaporation of approximately one pint of moisture per hour, and there must be a corresponding intake of water.

Marsh (1930) found in experiments on man that complete saturation with water vapour, if the surrounding air is at a temperature of 90° F., causes an immediate and uncontrollable rise of body-temperature. Pembry (1926) recorded the case of a man born without sweat-glands but otherwise healthy ; owing to abnormal rise in his temperature he was unable to do muscular work in summer in England unless his shirt had previously been soaked in water. People with ichthyosis are well-known to be intolerant of tropical temperatures, and a normal man treated with atropine in therapeutic doses is easily reduced to the same condition as one born without sweat-glands. Fatigue of the sweat-glands (Haldane) may be due to the low concentration of salt in the blood. A normal man of 60 kilos holds in his body no less than 40 kilos of water, of which about four are in the blood, and if water is slowly abstracted, it is replaced almost at once from the tissues. Men living in the Persian Gulf Littoral are exposed to a high atmospheric temperature varying between 125° F. and a minimum of 85° F. Hence, the European has to sweat continuously to keep his skin temperature at

such a level that the circulating blood can be sufficiently cooled. Under these conditions diuresis is so reduced that urine is passed perhaps only once a day.

The agent responsible for the phenomena of heat-stroke and heat-exhaustion is, of course, heat. Haldane originally demonstrated the importance of moist heat, that the wet-bulb thermometer was the most reliable guide, and that the limits of man's power of accommodation were passed when the temperature of still air (as shown by the wet-bulb) exceeded 90° F.

Moist heat is therefore the most important factor, while the air temperature, wind velocity, and relative humidity are all of importance (*see also* p. 11). In calm air the normal human body can support an air-temperature of 100° F. if the relative humidity is less than 90 per cent.; 120° F. if less than 40 per cent.; and 140° F. if less than 15 per cent. Rogers found that the mortality of patients with a temperature of 107° F. was 8·3 per cent.; with a temperature of 107° to 109° F. it was 29·2 per cent., and with a temperature of over 109° it was 69·2 per cent.

It is a matter of common observation that illness due to exposure to heat, in the absence of sunlight, is common amongst workers in deep mines, and stokers in the stokehold of steamships. On the other hand, the blue-violet rays in sunshine have a noxious effect on patients suffering from pellagra or smallpox, and cause photophthalmia and some blindness. A certain amount can be learned from the effects of high environmental temperatures upon animals occupying different levels in the biological scale. Thus, frogs suffer from "heat-stroke" when the temperature of the water rises to 104° F.; it has been found that the lactic acid concentration in the blood and muscles of this amphibian rises to such a height that it becomes completely paralysed. Guinea-pigs begin to succumb to heat-stroke when the shade temperature rises to 110° F., rabbits when it reaches 116° F., and man at 130° F. In such circumstances the body is exposed to heat of such intensity that the natural powers of cooling are overwhelmed, the body temperature rises, increasing the respiratory and nitrogenous exchange, causing not only retention of heat but also overproduction.

Martin showed that the tropical sun can produce local heating of the skull to a depth of one to two centimetres of the skull surface, hair and tissues.

Hyperpyrexia due to heat is complicated by the effect of sweating upon the concentration of salts in the blood, so that even in a cool atmosphere, heavy manual labour, causing generous perspiration over long periods of time, when associated with deficient salt intake will, in experimental individuals, produce severe symptoms which can be cured by salt ingestion (Moss, 1927).

It thus appears possible that suppression of the sweat mechanism is the primary factor in the production of heat-stroke.

Heat-exhaustion may occur in any climate, high atmospheric temperature being the essential factor. *Heat-hyperpyrexia* has a peculiar endemicity. The differences are summarized in Table V, p. 387.

HEAT-EXHAUSTION

Definition.—Sudden faintness, or fainting, brought about by exposure to high atmospheric temperature.

Ætiology.—The healthy human body can support with impunity very high atmospheric temperatures. In many parts of the world men live and work out of doors in temperatures of 100° or even of 120° F. The stokers of steamers, especially in the tropics, discharge for hours their arduous duties in a temperature often over 150° F.

When, however, the physiological activities have become impaired by disease, especially by heart, kidney, liver or brain disease, or by malaria, by alcoholic or other excess, by fatigue, by living in overcrowded rooms; or when the body is oppressed by unsuitable clothing; or in a combination of some of these factors—then high atmospheric temperatures are badly supported, the innervation of the heart may fail, and syncope may ensue.

Heat exhaustion is responsible for the fainting attacks seen in people in crowds on hot days, or soldiers standing on parade in the hot sun. It is a temporary, and usually not a serious, failure of the circulation to adapt itself to hot conditions.

Symptoms.—The patient feels giddy, and perhaps staggers and may fall. He is pale; his pulse is small, soft, and perhaps fluttering; his breathing is shallow, perhaps sighing, never stertorous; his pupils are dilated; his skin is cold; his temperature is subnormal; and he may be partially, more rarely quite, unconscious. Usually, after a short time, he gradually recovers; very likely with a splitting headache and feelings of prostration. In a small proportion of cases the faint is not recovered from, and death

Heat cramps occur in hot, dry conditions, and are associated particularly with radiant heat-boilers and furnaces. They are not associated with a rise in body temperature, but with excessive sweating, loss of chlorides, potassium and sodium ions. The calves are first affected, then the thigh muscles which are sore and aching. They can be prevented by saline drinks and a mixture of potassium, sodium and chlorine.

Hyperventilation tetany is produced by alkalosis of the tissues, and can be brought about by overbreathing due to heat.

Treatment.—In syncopal heat-stroke the patient should be laid at once on his back in a cool, airy and shaded place. His clothes should be loosened, a little water dashed on his face and chest, and ammonia held to his nostrils. If necessary, a stimulant may be given by the mouth, or injected into the rectum or hypodermically. It is a mistake to douche these cases too freely. The object is rather to stimulate than to depress.

HEAT-HYPERPYREXIA

Synonyms. Heat-stroke; insolation; thermic fever; siriasis; sun-stroke.

Definition.—An acute condition developing in high atmospheric temperature, characterized by sudden incidence of hyperpyrexia, coma, and extreme pulmonary congestion and œdema.

Geographical distribution.—Heat-hyperpyrexia appears to be remarkably restricted. Although this type has been reported in many countries, on careful investigation it will be found that a large proportion of the reputed cases are really other diseases, more especially cerebro-spinal fever, apoplexy, tuberculous [illegible] al malaria, or some other phase of acute disease, but not true heat-hyperpyrexia.

Table V

HEAT-STROKE

	Heat-Exhaustion (Syncope)	Heat-Hyperpyrexia
Onset.	Sudden faintness.	(*a*) *Prodromal* (not constant). Restlessness, vertigo, headache, mental confusion, anorexia, thirst, sighing, visual disturbances, nausea, vomiting, urinary irritability, suppression of sweat.
	Symptoms : Giddiness fainting, shock.	(*b*) *Symptoms :* Rapid hyperpyrexia, coma, pulmonary congestion.
Cause.	Exposure to high temperature, especially in stokeholds.	Direct action of solar or atmospheric heat on body causing auto-intoxication.
Face.	Pallor.	Flushed.
Pupils.	Dilated.	Contracted.
Pulse.	Small, soft, fluttering.	Rapid ; low blood pressure.
Respiration.	Shallow, sighing.	Stertorous.
Temperature.	Subnormal.	Hyperpyrexial.
Skin.	Cold and clammy.	Dry, sweat suppressed.
	No change.	Small quantity ; may be suppression ; offensive. Albumin, indican, R.B.C.'s present,
Clinical.		Sphincter control may be lost.
Reflexes.	Present.	Erratic.
Consciousness.	Partial or temporary loss.	Coma.
Death.	Rare.	Mortality varies with temperature.
Treatment.	Stimulation. Lay patient in cool place ; brandy ; ammonia to nostrils, etc.	Rapid reduction of temperature ; cold bath, ice packs, continuous spray, normal saline intravenously ; chloral or pot. bromide if restless. Stimulate only after sweating begins. Artificial respiration. Lumbar puncture.
.	Douching too freely.	Reduction below 102° F.

The endemic areas are :—in America, the east coast littoral of the United States, more especially in the great towns, the Mississippi valley, the coast of the Gulf of Mexico, the valleys of the Amazon and of the La Plata, and the South Atlantic coast ; in Africa, the valley of the Nile, the coasts of the Red Sea, and a low-lying part of Algeria near Biskra ; in Asia, Syria, Iraq, the valleys of the Indus and Ganges, South Persia, Lower Burma, Tonquin, and South-East China ; in Australia, the Murray River district, the Queensland coast, and possibly the plains of Sydney. It is not met on the high seas, although it is well known on ships in the narrow, landlocked Red Sea and the Persian Gulf. During the 1914–18 war dangerous cases occurred most numerously in Iraq, especially during July, 1917, when for three days the temperature reached 122° F. in the shade, and 135° F. in the interior of double fly-tents.

During the present war the effects of heat on troops has been studied in Persia and Iraq and is the subject of an official memorandum (1943).

Ætiology.—New-comers to the endemic areas and Europeans are more liable than natives or residents of long standing, and men over forty than those younger. All ages and both sexes are susceptible ; but in consequence of their habits and more frequent exposure to the predisposing and immediate causes, men are more liable than women.

Heat-hyperpyrexia is generally attributed to direct action of atmospheric or solar heat on the body. Many theories of the *modus operandi* of this cause have been advanced. Among these may be mentioned superheating of the blood by the high temperature of the surrounding atmosphere. Hearne pointed out that heat-hyperpyrexia is associated with suppression of sweat, which may precede the onset of serious symptoms by 48 hours, for after prolonged exposure to high temperatures the sweat apparatus becomes exhausted and the glands cease to function. Coma, delirium and convulsions appear directly the body-temperature reaches 108° F. Hypodermic injections of atropine have been shown to predispose to heat-hyperpyrexia through its action upon the sweat-glands ; somewhat similar results have been produced in lower animals by Cramer, by injection of β-tetra-hydronaphthylamine, which over-stimulates the thyroid-adrenal apparatus. The cramps are attributed to the coagulation of myosin in the affected muscles (Cajamian).

Blood chemistry.—Marked dehydration is associated with an increase in the percentage of hæmoglobin, sometimes to 110 per cent., and a corresponding increase in the red blood-cells. The leucocyte count is also slightly increased. There is a diminution of the blood chlorides and plasma bicarbonate, but a rise in lactic acid, blood-sugar and, usually, blood-urea (Marsh).

The earliest sign of hypochloræmia is low, or absent, urinary chlorides. The test is performed as follows :—To 10 drops of a 24-hour specimen of urine is added one drop of 20 per cent. potassium chromate solution ; this gives a canary yellow colour. Silver nitrate (2·9 per cent. solution) is added, drop by drop, until the colour changes suddenly to brown. The number of drops of silver nitrate equals the amount of sodium chloride, in grammes per litre. Sugar and acetone are occasionally found in the urine, and also a trace of albumin and a few hyaline casts.

Pathology.—The cause of death is usually circulatory failure. A notable feature of fatal hyperpyrexia is the early appearance of rigor mortis. The blood is remarkably fluid, or but feebly clotted. The venous system is loaded, dark fluid blood pouring from the phenomenally engorged lungs and other viscera on section. Both blood and muscles are said to yield an acid reaction, more or less pronounced. The red blood-corpuscles are crenated and do not form rouleaux. If the post-mortem examination is made shortly after death and before decomposition changes have set in, the heart in early rigor mortis, particularly the left ventricle, will be found remarkably rigid ; this is sometimes described as being of "woodeny hardness." There may be some venous congestion of the meninges, and the brain shows small multiple hæmorrhages. On microscopic examination, necrotic changes in the ganglion cells, with chromatolysis of the nuclei, are found. The cerebro-spinal fluid is clear and under pressure. Cortical changes in the suprarenals have been described. In the lungs there is hæmorrhagic pulmonary œdema. The intestinal mucosa, as well as that of the stomach, is swollen, and exhibits patches of congestion. The temperature of the cadaver continues to rise after death, and may reach 114° F.

Symptoms.—Recent workers on this subject recognize the importance of the *subacute effects of heat.* The onset is insidious, with pyrexia, lassitude, headache, nausea, and vomiting, giddiness and insomnia. The mentality changes to dullness or irritability. Signs of dehydration begin to appear, and the amount of chlorides in the urine is diminished. This state usually lasts 7–10 days.

Among prodromata of a major attack, which may show themselves with greater or less distinctness for an hour or two, or even for a day or two, are great disinclination for exertion, pains in the limbs, drowsiness, vertigo, headache, mental confusion, sighing, anorexia, thirst, intolerance of light —sometimes accompanied by chromatic aberrations of vision—suffused eyes, nausea and perhaps vomiting, præcordial anxiety, suppression of sweat, urinary irritability, sometimes a sense of impending calamity, an hysterical tendency to weep, and a quickened pulse.

Acute heat stroke.—The first indication of anything seriously wrong may be a short stage of restlessness, or possibly of wild delirium. This brief preliminary stage rapidly culminates in coma and high fever, quickly passing into hyperpyrexia which may reach 112° F. The pupils are contracted, except immediately before death when, along with the other sphincters, they relax. The face is congested and the muscles rigid. The reflexes are partially or wholly in abeyance. There may also be, especially in the graver cases, free watery purging, the dejecta as well as the skin of the patient emitting a peculiar and distinctive mousy odour. The scanty urine may contain indican, blood-corpuscles, albumin and casts. The cerebrospinal fluid is normal in appearance and its pressure slightly raised.

Willcox distinguished different clinical types of heat-hyperpyrexia :

(1) *Gastric type.*—A most deceptive form, in which the axillary temperature is normal, the rectal temperature raised, and gastric symptoms predominate, with congestion of the liver. Fatal hyperpyrexia may develop without previous warning.

(2) *Choleraic type.*—This form is sudden, with purging and general resemblance to true cholera ; it may be fatal within three or four days. The rectal temperature may rise to 110° F. after death.

(3) *True heat-hyperpyrexia,* in which nervous symptoms predominate, as described, accounts for 70 per cent. of the cases. The temperature may rise to 118° F. for a short time, and the patient yet recover (Marshall).

Unless active measures to lower temperature are taken early and vigorously carried out, in the great majority of instances death will occur within a few hours, or even minutes, of the onset of insensibility. The immediate cause of death is generally the failure of respiration. Rarely do cases linger for a day or two. Partial recovery is sometimes followed by relapse. In favourable cases the disease usually terminates by crisis. Convalescence is rapid. Unless the patient is moved into different surroundings a relapse may occur; two or even three have been recorded. Occasionally cerebral or cerebellar symptoms may persist.

The death-rate may be materially reduced by early and judicious treatment. In Iraq during the 1914–18 war, the case-mortality among British troops was about 8 per cent.

Diagnosis.—The high fever is sufficient to differentiate heat-hyperpyrexia from sudden insensibility caused by uræmia, by diabetic coma, by alcoholic and opium poisoning, and by all similar toxic conditions. Carbon monoxide and hydrogen sulphide poisoning must also be thought of. Cerebral hæmorrhage, particularly pontine, may, after some hours, be followed by high temperature; but here the febrile condition follows the insensibility, whereas in heat-stroke the febrile condition precedes insensibility. Diagnosis from a cerebral malarial attack may be very difficult; chief reliance has to be placed on the history, if obtainable, on the condition of the spleen, and especially on the result of microscopic examination of the blood; but sometimes the subtertian parasites may not be demonstrable for two or even four days from the onset. Malarial fevers and the early stages of the eruptive fevers in children are very apt to be regarded as heat-stroke, particularly if there has been recent exposure to a hot sun. Cerebro-spinal fever, so often mistaken for heat-hyperpyrexia, may be recognized by the occipital retraction, the irregular pupils, the frequent occurrence of strabismus, Kernig's sign, the comparatively low and fluctuating temperature, the associated herpes, the initial rigor, and its duration. Lumbar puncture will, of course, give a clear differentiation. The fluid is often under high pressure, but is clear in heat hyperpyrexia, and lumbar puncture should be performed in these cases, not only for diagnosis, but as a therapeutic measure. Uncomplicated heat-stroke is accompanied by hypochloræmia, dehydration, absence of urinary chlorides, excess of lactic acid, and low content of bicarbonates in the blood.

Marsh states that during a heat-wave in the Persian Gulf mild cases of heat-exhaustion are usually in the majority, and so it is difficult, sometimes, to distinguish cases of pure fright from genuine cases. Real cramps constitute a valuable diagnostic sign. They are so extremely painful that the patient cannot sustain a conversation and the affected muscles can be felt forcibly to contract.

Men of fifty years of age or over, or young men who have been suddenly introduced to a hot climate, should be carefully examined, for they may develop rapid hyperpyrexia without any of the usual premonitory signs. The correlation of heat deaths with increasing age is probably due to progressive diminution in the heart reserve.

Treatment.—Treatment must be instituted at the earliest possible moment. A few hours' delay may mean death to the patient. In all fulminating fevers, including heat-hyperpyrexia, in warm climates, if malaria be suspected, particularly if the subtertian parasite be discovered in the blood, quinine should be injected intravenously or intramuscularly at once (7–10 gr. of the dihydrochloride), or given by enema as directed for malaria; this dose should be repeated three or four times at intervals of four hours. Should there be any suspicion of alcohol poisoning, the stomach should be washed out. In every case of heat-stroke, whether it has been deemed advisable to administer quinine or not, attempts must at once be made to reduce temperature by such rapidly acting measures as the cold bath, or ice applied in various ways to the head and body. The patient should be placed on a wet sheet supported upon bed cradles, thus forming a moist chamber in which he lies; the whole may rest upon a rush-covered bed or "angareeb." Mackintosh sheets must be avoided. The continuous water-spray with iced water, together with an electric fan, simulates the natural process of sweating to the best advantage. In the absence of electric fans an iced wet sheet may be wafted up and down over the patient's abdomen by a punkah-like arrangement. Rubbing the skin with ice, by constricting the capillaries, apparently only obstructs evaporation. A thermometer should be kept in the rectum and the application of cold should be discontinued as soon as the thermometer in the rectum has sunk from 106° to 102° F., or from 109° to 104° F. If powerful antipyretic measures are carried beyond this point the fall of temperature may continue below the normal, even as low as 91° F., and dangerous collapse ensue.

Fluid must be given in large quantities, as 0·25 per cent. saline drinks or, if the patient cannot swallow, as intravenous normal saline, of which quantities up to 20 pints may be given. The fluid and salt requirements are regulated by the appearances of dehydration, the blood concentration (estimated by red cell count and percentage of hæmoglobin), the amount of urine and the blood pressure. Intravenous saline is indicated if the systolic blood pressure is below 100. It must be given with great care, for the cardio-vascular system may be unable to deal with it. If the blood pressure does not rise, the patient may die of pulmonary œdema, which may occur after 9 pints has been administered.

A balance sheet of fluid intake and output should be kept, and fluid should be given in large quantities until the total output balances the total intake. In this balance sheet at least 8 pints must be allowed for daily loss of fluid by the sweating of a man at rest.

On discontinuance of the iced sheet, the patient should be wrapped in a dry blanket; very likely, perspiration, a favourable sign, will then set in. Stimulants may now be necessary. Strychnine, owing to the marked tendency to convulsions in heat-stroke, must on no account be used as a cardiac stimulant; Chandler, as the result of his large experience, recommended the injection of 40 min. of tincture of digitalis. Convulsions are best controlled by cautious venesection. As death in heat-stroke generally results from failure of respiration, Hearne and others strongly recommended artificial respiration when the breathing threatens to become suspended; it should be maintained for half an hour or longer. Lumbar puncture is indicated as a rational method of relieving intracranial pressure. Gastric cases should receive a liberal supply of bicarbonate of soda—30 gr. every two hours. Diarrhœic and dysenteric cases are specially liable to hyperpyrexia because of loss of fluid. Nourishment is needed; sweetened diluted tinned milk may be used.

During convalescence great care must be exercised to shield the patient from all influences calculated to provoke relapse. The power of sweating may be in abeyance for three weeks or longer.

Sequelæ.—Permanent damage resulting from heat-stroke is rare. Temporary loss of memory and lack of concentration commonly occur, but sometimes cerebellar manifestations, epilepsy, hysteria, tachycardia and myocardial injury have been described.

Prophylaxis.—Patients in hospital are especially liable to heat-hyperpyrexia. The most valuable practical method is to attempt to forestall it by periodically inspecting the patients to find out those with commencing suppression of sweat, urinary irritability, restlessness and insomnia.

A heat-stroke hut, or treatment room, or even a heat-stroke ward, is a most desirable addition to hospital equipment in the tropics.

A special refrigerating apparatus consists of a horizontally placed ammonia compressor working in conjunction with a brine-circulating system. At Masjid-i-Suleiman in South Persia (Anglo-Iranian Oil Fields) heat-stroke cases and, indeed, all cases of fever, are, in outlying stations during the heat of the day until the cool hours between midnight and five a.m., kept in a cold-storage chamber attached to the ice-plant. During the coolest part of the night they are put into a fast ambulance and taken to the nearest heat-stroke hut where they are kept until complete recovery has taken place. Such accommodation should be provided for 10 per cent. of the population exposed to risk, in order to provide for the rush of cases during a heat wave.

Buildings must be so constructed that they do not retain heat, and cool down quickly. The roof should be double, enclosing a wide air space, or it should be of thick thatch, projecting well and shading the upper walls. A ventilated verandah should extend all round, supporting hanging curtains of strong canvas, surfaced on both sides with aluminium foil. Double walls should be provided. A tropical helmet with aluminium foil in the crown should be worn (*see also* p. 17).

Efficient methods of cooling the air are employed in industry in many parts of the world. These include methyl chloride or ammonia refrigerating machines, or the cooling powers of evaporating water at atmospheric temperatures and in *vacuo*. Air-conditioning of houses and dwelling-rooms is commonly found in New York and other American cities, and the matter is solely one of expense.

The cost, according to Rennie, of maintaining a cool chamber, is £400-£500 per annum.

The drink available for all workers in endemic areas of heat-stroke should consist of : sodium chloride 6 oz., potassium chloride 4 oz., water 1¾ pints. Of this concentrated solution, 17 fluid ounces are added to 8 gallons of water for drinking ; a flavouring may be added (Dunlop, McNee and Davidson).

As the result of these measures heat-stroke has been greatly reduced and has almost ceased to count as a cause of invalidism.

Acclimatization.—Some organizations in the tropics endeavour to avoid the ill-effects of heat by ensuring fitness and acclimatization of the workers. In the Witwatersrand gold mines, candidates for employment are subjected to an *exercise tolerance* test in rooms artificially heated to 94° F., wet-bulb, and are then graded on their reactions, suitable candidates being put through a further course involving exposure to high temperatures in stages and lasting, sometimes, for fourteen days. Soldiers should be given lectures on the precautions necessary in hot climates.

Fewer casualties occur from heat among men born and bred in the hot climates than among those reared in temperate climates. While there is a general agreement that excessive alcohol consumption is contra-indicated, less attention has been paid to the profound effects that may arise from shortage of water and to the importance of replacing salt lost in sweat. The minimum daily fluid requirement in the hot season is 10 pints, and a man doing hard manual work may take 4 gallons. A daily ration of $\frac{3}{4}$ oz. of salt is essential, and should be taken for several days before entering a heat stroke area, and continued throughout residence there. There is no evidence that alcohol in moderation is harmful. Constipation in the hot season is almost physiological and must be avoided, but care should be taken that when saline purges are given, plenty of fluid is drunk, since a watery motion may induce dehydration, and a patient may be constipated because he is already somewhat dehydrated.

In the present war it has been noted that, during the hot weather of 1942, nearly three-quarters of the cases of general effects of heat amongst troops in Persia and Iraq occurred before, during and after disembarkation. Many could have been prevented had adequate precautions been taken on board ship. High atmospheric humidity with a wet bulb temperature of 83° F. is the danger point.

It is dangerous for persons who have suffered from heat hyperpyrexia to return to the conditions or surroundings that brought it on in the first place.

SECTION II

VITAMIN DEFICIENCY DISEASES

(Avitaminoses)

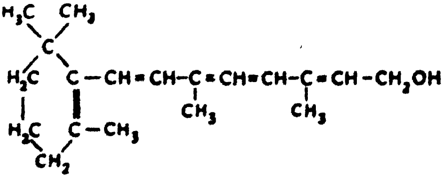
Preliminary statement.—The term avitaminosis is applied to a series of apparently quite distinct clinical conditions in which the main ætiological factor is in the dietary. It is not the quantity, but the imbalance of ingredients which may bring about such serious metabolic changes. The process must be regarded as quite distinct from starvation. Dietetic deficiencies are due to the gradual withdrawal of ingredients necessary for the elaboration of intricate biochemical processes essential to the maintenance of life. The exact chemical constitution of some of the vitamins has been determined and several have been synthesized. Though small in quantity their influence upon metabolism is profound. For the comprehension of tropical deficiency diseases an outline of vitamin physiology must be given, but it is manifestly impossible to give a full account of this rapidly expanding subject.

Vitamins are regarded as catalysts, and they are concerned with the metabolism of carbohydrates and other essential substances. The modern conception is that the same clinical phenomena may result either from actual deficiency in the diet or from lack of absorption from the bowel. Possibly some vitamins may be destroyed in the body by the toxins of disease.

VITAMIN A

This includes A_1 found in animals and sea fish, and A_2 found in fresh-water fish. "Provitamin A" denotes those plant carotenoids which are converted by animals into vitamin A.

The most striking effect of vitamin A deficiency is night blindness, which can be cured—often in twelve hours—by eating liver, which is rich in vitamin A. Conjunctivitis and xeropthalmia are the most noticeable examples of the change in epithelial surfaces of the body brought about by lack of vitamin A. The term "anti-infective" vitamin was bestowed on vitamin A by Green and Mellanby, because they found that animals killed by lack of it showed multiple foci of infection in those areas where the epithelium had been affected. The carotene content of plants has been found to vary with their vitamin A potency. The accepted formula for vitamin A is:



The synthesis of pure vitamin A was effected in 1937. The crystals are pale yellow, melting at 5·5°–6° C. to a viscous oil. Vitamin A gives a band of maximum absorption in the ultraviolet region of 328 millimicrons. It and its carotenoid precursors are fat-soluble and are concentrated in the unsaponifiable extracts of fats. They give the Carr-Price colour test: antimony trichloride dissolved in chloroform with vitamin A rapidly develops a blue colour which then fades.

In biological estimation of vitamin A, either the curative or prophylactic method is used. This is based upon growth response in young rats. The diet should contain all essentials, apart from vitamin A, so that arrest and resumption of growth can be attributed with certainty to the vitamin content alone. Absorption spectrum estimations of vitamin A have been found reliable, producing results more or less in harmony with biological estimations, but these must be converted into international units. Estimations based on colour reactions, " Lovibond blue units," do not give such accurate results as the biological and physical estimations.

A definite weight of β-carotene is used for the International Unit since it is converted in the body to vitamin A. The International Standard for vitamin A is the " Reference Cod-Liver " oil of the U.S. Pharmocopeia which contains 3,000 I.U. per grm. The International Standard unit is 1γ (0·001 mg.); 3 to 5γ daily are sufficient to protect young rats.

Vitamin A is formed in the body from certain red or yellow plant pigments known as carotenoids. No animals can synthesize them for themselves, nor form this vitamin from any other source.

Carotene, $C40\ H56$, a hydrocarbon, is widely distributed, being found in bacteria and higher plants ; its value to plants is obscure, but it is usually found in association with chlorophyll. The amount of absorption of carotene from various foods differs : only about 20 per cent. of the carotene of raw carrots is absorbed. Fat and bile are necessary for its absorption. The transfer of carotene across the wall of the gut probably depends on the formation, with bile, of a water-soluble diffusible complex. Carotene is stored in the Kupffer cells of the liver. The conversion of carotene to vitamin A takes place in the liver by the action of an enzyme—*carotinase*. Herbivorous animals depend entirely on carotene for their vitamin A, but omnivorous animals, like man, obtain it partly from carotene and partly from animal food in which the vitamin is present.

Diseases may affect storage by increasing utilization and hindering conversion of carotene to vitamin A, or by impairing the storage capacity of the liver. Vitamin A is never excreted by man in good health except as a breakdown product.

Hypervitaminosis A and excess of carotene.—Few bad effects have been reported from taking too much vitamin A, though doses from 60,000—200,000 I.U. are in common use. High carotene levels in the blood decrease resistance to respiratory infections and occasionally cause *Xanthosis cutis* (or carotinæmia). This is a condition, not uncommon in the tropics, where the skin, but not the conjunctiva or the urine, becomes yellow from deposits of carotene ; it may at first sight suggest jaundice. Diabetics on the wrong dietary are likely to develop carotinæmia.

Distribution of vitamin A.—The provision of vitamin A in human diet is important ; it is found in very few foods, of which the most common are butter, eggs, milk, honeycomb, liver and some fish and fish liver oils. Of these, the first three are the most widely consumed, but their vitamin A content is by no means constant and in turn depends entirely on the diet of the cows and fowls. The colour of the egg yolk affords a good index to the amount of carotenoids. Fish liver oils are extremely rich in vitamin A, and constitute the only concentrated medicinal preparations in use.

Carotene and provitamin A are widely distributed in vegetables and fruits, in association with chlorophyll, and in yellow vegetables and fruit.

In tropical and subtropical countries, such as the Philippines, the Dutch East Indies, Ceylon, India, China, the West Indies and parts of E. Africa, the problem of child blindness is widespread owing to lack of vitamin A.

Domestic cooking causes no appreciable loss of vitamin A or carotene, but prolonged boiling of milk is harmful. The maximum human requirements of vitamin A or carotene are 60 I.U. per kilo of the former and 200 I.U. of the latter daily, which means for a man of 11 stone 4,200 I.U. and 14,000 I.U. respectively. For normal growth and freedom from clinical symptoms, 20 I.U. of vitamin A and 40 I.U. of carotene daily per kilo body weight are needed. These needs are increased during pregnancy and lactation. As a general rule, most pathological conditions of the bowel interfere with the absorption of carotene from the bowel or its conversion to vitamin A in the liver and to a much smaller extent with the absorption of vitamin A itself.

All diseases which interfere with digestion of fat hinder the absorption of both carotene and vitamin A, and indeed the former is said not to be absorbed in coeliac disease or, probably, in sprue.

Deficiency of vitamin A.—Human vitamin A deficiencies can be recognized by: (1) clinical examination; (2) measuring dark adaptation; and (3) estimating vitamin A in the blood.

The popular conception that children require more of this vitamin than adults is not correct; rather the reverse appears to be true. Vitamin A seems to be necessary, not so much for the metabolic activities of the cells as for the maintenance of their structure. A plentiful supply appears to increase longevity and delay senility. The effects of vitamin A deficiency are seen especially in the epithelial surfaces of the body and their replacement by stratified, squamous, keratinizing epithelium. Some tissues are damaged earlier than others by this deficiency. In general, the changes are not very pronounced in the glands, but the epithelium lining the ducts of the glands is involved before that lining the acini. This accounts for the common occurrence of abscesses, or cysts, at the base of the tongue, which are really salivary retention cysts that may become infected. All the respiratory tract, the nasal sinuses, and the Eustachian tubes are involved. In the lungs the smaller bronchi become plugged with desquamated cells, thus paving the way for infection.

Vitamin A is essential for the germinal epithelium of the testes. The earliest changes arising from deprivation are sloughing of the germinal cells into the lumen of the tubules and a gradual reduction of their size. These are independent of the action of the pituitary.

The mucous membrane of the digestive tract is not involved, but there is some evidence that lack of vitamin A interferes with the function and structure of the gastric glands and pancreas.

This avitaminosis causes hyperplasia and keratinization of the gums, whilst developing teeth are severely damaged, by deprivation of the odontoblasts of some controlling influence over their growth, leading to poor or deformed denture.

The Kidneys.—Vitamin A plays an important part in urinary secretion. There are several possibilities: (*a*) the kidney acts as a storehouse for vitamin A; (*b*) it destroys or excretes excess of vitamin A; (*c*) A is necessary or the functioning of the kidney; (*d*) impaired renal function allows vitamin A to leak away in the urine.

The Endocrine System.—The relationship of vitamin A to the endocrine system is still uncertain. Probably the thyroid stimulates the conversion of carotene to vitamin A and, conversely, the latter decreases the effect of thyrotoxine in stimulating metabolism.

The skin.—The skin changes which occur as a result of vitamin A deficiency were described by Nicholls as toad skin or *phrynoderma.* Many have recognized a close association between skin changes, night blindness and xerophthalmia. The dry skin is followed by a sudden local eruption which spreads over to front and sides of the thighs, the posterior and lateral sides of the forearms, just below the elbows, the fronts of the arms and shoulders. The scalp is not affected, but the hair may be dry and brittle and the nails may have transverse or longitudinal ridges. The eruption consists of dry, horny, round or oval sharply-defined papules, varying in diameter from that of a pin's head to a quarter of an inch, and the size increases with the duration of the deficiency. Each papule is formed by hyperkeratosis of the pilo-sebaceous follicles, has a hard keratinous core and seldom, if ever, undergoes pustulation. Treatment with vitamin A is entirely successful. The first sign of recovery is a return of sweating, so that the skin within two or three weeks no longer feels dry.

The eyes.—The earliest detectable result is slight impairment of dark adaptation; a severe deficiency leads to night blindness or hemeralopia. In bright light, vision is effected by the cones of the retina, which are not affected by lack of vitamin A. When the light is suddenly decreased, the eye cannot see for a moment, until dark adaptation occurs: this increase of sensitivity is due to transference of the function of vision to the rods of the retina, which are not stimulated directly by light, but only indirectly through the chemical changes caused by light in the visual purple of which vitamin A is a component. On the rapidity with which visual purple is re-formed depends the rapidity of dark adaptation. Shortage of vitamin A must slow down the formation of visual purple and therefore dark adaptation. The measurement of this factor has been extensively used in nutritional research for estimating vitamin A deficiencies.

Either the Birch-Hirschfeld photometer or the Jeans-Zentmire biophotometer is used. The eyes are first exposed to a bright light, which causes a uniform bleaching of the visual purple, after which the light is extinguished and the patient is shown small test spots of light. As the eyes become adapted to the dark, so the illuminations of the test spots can be reduced without making them invisible. The lowest illumination which, after ten minutes, allows the spots to be seen is taken as the measure of dark adaptation. The results are sufficiently accurate to divide patients into normal and subnormal groups.

The first change in the eye is a drying or xerosis (*xerophthalmia*) which is usually accompanied by photophobia. This is due to metaplasia of the conjuctival epithelium, stopping the secretion of mucous cells; it is confirmed by finding keratinous cells in gentle scrapings of the eye. No further changes may occur, or this may be followed by photophobia, lachrymation and a sticky discharge. The cornea may become œdematous, and necrotic, so that keratomalacia follows. Recovery, apart from scarring of the cornea, is always possible, if perforation has not taken place. Prolonged mild deficiencies lead to formation of "Bitot's spots." These are always placed just lateral to the cornea on the equator of the eye, and are generally triangular with a slightly concave base, and about 5 mm. in width, though sometimes they are round or oval and may be composed of lines and dots. Nicholls and Nimalasuriya in Ceylon described the lesions as resembling "a dab of chalk paste striated with a pin." They never occur on the cornea itself.

Treatment is with large doses of cod-liver oil or vitamin A concentrates, but recovery is slow.

The nervous system.—Deprivation of vitamin A causes degeneration of the nervous system, though the process is usually surprisingly severe before clinical symptoms are observed. It was suggested by Mellanby that *lathyrism* (*see* p. 783) is a disease not only due to the eating of a vetch—*Lathyrus*—but also to lack of vitamin A.

Moreover, beriberi is accentuated by this deficiency and there is some evidence that vitamin A has some action in protecting the nervous system against the effects of ergot.

Other effects of lack of vitamin A are respiratory infections and diarrhœa.

Measuring the lack of vitamin A in the blood.—The normal values for vitamin A in the blood are probably between 100 and 300 I.U. per 100 c.c. On the whole, values tend to be low in the early spring. Estimations of carotene in the blood are not of great clinical value, since carotene is useless to the body until converted to vitamin A. High carotene levels may be present with an A deficiency, as in myxœdema. The methods employed for estimation of vitamin A and carotene in the serum are based on the antimony trichloride colour reaction and matching the depth of the colour of the carotene against solutions of potassium bichromate or coloured glasses; this process has been greatly assisted by the introduction of the photocolorimetric method.

THE VITAMIN B COMPLEX

What was formerly known as the vitamin B complex is now shown to consist of two factors, one thermolabile and the other thermostable. The historical sequence of the main discoveries is outlined on pp. 414.

The following are now recognized:

Vitamin B_1 (Aneurin, Thiamine).
Vitamin B_2 (Riboflavin).
Vitamin B_3 Nicotinic acid (Niacin), a factor essential for the growth of pigeons).
Vitamin B_6 (rat anti-dermatitis factor or adermin).

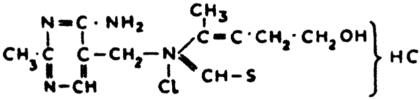
Other allied vitamins.—*Vitamin H* (Biotin) has been isolated from liver and shown to be a cyclic urea compound containing sulphur with one carboxyl group. It is essential for the normal functioning of many micro-organisms and higher animals, and is present in high concentration in tumour tissue.

Choline is important as an accessory food factor and in maintaining normal kidney structure. It is always present in concentrations of the vitamin B complex.

Adenylic acid, a complex of adenin, ribose and phosphoric acid, is widely distributed in nature and is extracted from yeast. It is a " respiratory mediator " forming part of the enzyme system concerned in catalyzing the oxidation-reduction mechanism in the living cell. Spies and his colleagues found that ulcers in the mouths of malnourished patients healed after intravenous injection of 50 mgm. of adenylic acid twice daily.

Pantothenic acid is the chick anti-dermatitis factor and is one of the filtrate factors necessary for the growth of rats. It is found mostly in brewers' yeast, liver and eggs, wheat bran and split peas. There is some reason for believing that it is associated with riboflavin metabolism, but its exact rôle in human nutrition is not known with certainty, though it is assumed to be necessary. Pantothenic acid is of extremely low toxicity. Its level in the blood of patients suffering from deficiency diseases (beriberi, pellagra) is 23–50 per cent. less than normal.

Vitamin B_1 (*Aneurin : thiamin*).—Vitamin B_1 has the following structure:



composed of pyrimidine and thiazole nuclei. It is therefore 2-methyl-5-(4-methyl-5-β-hydroxethyl-thiazolium chloride)methyl-6-amino-pyrimidine hydrochloride ($C_{12}H_{17}ON_4S$), a colourless water-soluble crystalline substance containing a molecule of water of crystallization and melting at 248–250° C. In dry conditions it is stable at 100° C. for twenty-four hours. The rate of destruction is increased by presence of water and alkali. It is oxidized to thiochrome by potassium ferricyanide in the presence of alkali.

Destruction in ordinary cooking processes is not very great if soda be not added to vegetables. Pressure cooking, even when rapid, causes considerable destruction. The destructive action of sulphites is of some importance, since these are used in the preservation of fruit pulp and juices, and depends on the *p*H of the medium. In canning there should be little loss. Vitamin B_1 is destroyed on autoclaving, and largely inactivated when yeast and liver are subjected to heat under pressure. When subject to mild oxidization with potassium ferricyanide the alkaline solution is converted to *thiochrome* which exhibits intense blue fluorescence under ultra-violet light, a reaction employed in the estimation of B_1. Thiochrome is devoid of any vitamin-like action.

B_1 is widely distributed in raw foodstuffs, the richest sources being whole cereals, especially the pericarp and germ (*see* p. 416), yeast, pork and pulses. Vegetables, including potatoes, are an important source. The diet of the working classes in Britain is so deficient in B_1 that white could with advantage be replaced by wholemeal bread. Yeast is an exceptionally potent source and should be used as a dietary supplement when large quantities are required. Milk is a poor source.

The physiology of B_1.—The original suggestion of Funk that B_1 plays some part in carbohydrate metabolism has been substantiated. Two of the intermediate products of the metabolism are lactic and pyruvic acids. Glucose is not directly oxidized in the body, but is transformed into carbon dioxide and water in a number of stages during which lactic and pyruvic acids are produced. B_1 deficiency in animals results in incomplete metabolism and is associated with increased urinary excretion of lactic acid. The blood level of lactic acid appears to be abnormally high in beriberi patients.

The work of Peters and his associates has shed much light upon the rôle of B_1 in carbohydrate metabolism. They were able to demonstrate increased lactic acid and diminished oxygen consumption in the lower part of the brain of pigeons suffering from B_1 avitaminosis. B_1 deficiency is associated with increase of pyruvic acid in the blood and its presence can be demonstrated by increase of the *bisulphite binding power* (B.B.S.) of the blood. Being a ketonic acid, pyruvic acid ($CH_3.CO.COOH$) combines with sodium bisulphite. In human cases of beriberi Platt and Lu demonstrated raised B.B.S. in blood, urine and cerebrospinal fluid. It is also claimed that the blood pyruvate of rats runs parallel with the degree of B_1 deficiency, as measured by the bradycardia test.

It is now generally believed that vitamin B_1 must first be converted into its pyrophosphoric ester before it acts as a specific catalyst necessary for the breaking down of pyruvic acid. The neurological lesions of B_1 deficiency are probably due to inability of the body to metabolize glucose efficiently. This oxidization can also be inhibited by alcohol, anæsthetics and barbiturates.

Vitamin B_1 and fat metabolism.—A diet rich in carbohydrate brings on symptoms of avitaminosis more rapidly than one containing much fat. B_1 may function as a co-enzyme in the synthesis of body fat from ingested carbohydrate and is therefore needed in greater quantities.

Other functions of B_1.—Vitamin B_1 may be associated in some way with thyroid function. After prolonged deficiency, structural changes in the thyroid have been observed, characterized by increase in colloid and reduction of active tissue ; experiments have shown that B_1 is antagonistic to thyroxine.

B_1 appears to potentiate the action of acetylcholine in the tissues by inhibiting cholinesterase, an enzyme which hydrolyses acetylcholine and checks its action as a parasympathetic hormone. It has also been shown to be a growth factor in plants and bacteria and also in infants.

Pharmacological action.—Subcutaneous injections of from 50–500 mgm. per kilo cause an increased oxygen intake of 20 per cent. in guinea-pigs within half an hour. B_1 also produces diuresis which is thought to be of central origin. Toxic effect occurs only when very large doses are given. Man will tolerate intravenous injections of 500 mgm. daily for one month. Because of the great difference between therapeutic and toxic doses and lack of cumulative toxicity, B_1 can be regarded as a particularly safe therapeutic agent for prolonged use.

Cowgill (1939) proved that man is unable to synthesize B_1, or store it to any appreciable extent. In experimental animals signs of deficiency may be produced in a period of 10 days to 3–4 weeks, but symptoms in *man* may appear after a few weeks of inadequate diet. It is readily absorbed from the small, and possibly also the large intestine but, even when ingested in sufficient quantities, it may escape absorption in certain digestive disturbances, such as vomiting and diarrhœa, or destruction of intestinal mucosa (chronic bacillary dysentery, ulcerative colitis). Diseases associated with diuresis may wash considerable quantities of B_1 from the tissues before it can be utilized. Absorption occurs by simple diffusion.

The larger part of B_1 is stored in the liver, kidneys and muscles, and it is abundant in the normal heart. Depletion occurs most rapidly in the muscles and is slowest in the brain. B_1 is excreted in the urine, and the kidney concentrates it from the plasma to a marked degree, perhaps twenty times or more, but it appears that only a small proportion of the vitamin given by the mouth or by injection is excreted in the urine, the rest being destroyed in the body. It is also excreted in the milk but no appreciable quantity in the fæces. Harris and Leong (1936) believed that excretion of less than 12 I.U. per day in the urine is evidence of B_1 deficiency.

Human requirements.—An increase in metabolic rate increases B_1 requirements. Thus, beriberi is more prevalent amongst stokers than sailors, owing to their greater physical exertions. Similarly, males suffer more from beriberi than non-pregnant women, due to harder physical work. In Manila there is a high incidence of beriberi among pregnant and nursing mothers. As the metabolic rate rises during fever there is apt to be an association of beriberi with malaria and other pyrexias.

The International Unit is the antineuritic activity of 3γ of pure B_1 (i.e. 333 I.U. = 1 mgm.). The minimum daily B_1 requirement in international units is expressed in Cowgill's formula: daily calorie intake 0·0284 × weight in kilos × 0·05. Therefore, for an adult of 70 kg (11st.) on 3,000 calories a day the minimum requirement would be approximately 300 I.U. or 1 mgm. The figure is the physiological minimum, but 500–700 I.U. (1·75 mgm.) is the desirable intake. The metabolic rates in pregnancy, lactation, infancy and childhood, per unit of body surface, are greater than in normal adult life, therefore a greater B_1 requirement is necessary. Infants require approximately 50–60 I.U. (0·2 mgm.). Up to adolescence the B_1 requirements increase with age. In hyperthyroidism and during exercise the B_1 requirements are increased.

Methods used for estimating B_1 in body fluids:

Bradycardia method.—Young rats are put on a B_1 deficient diet and, after three weeks, when they are losing weight, electrocardiograms are taken. The heart beats have now fallen from 500–550 a minute to 350. A test dose of the substance to be estimated is fed to the animal, which is then replaced on the basal diet. Another electrocardiogram is taken twenty-four hours later. The effect of feeding B_1 is to raise the heart rate, and the increase in rate and time over which the increase lasts are proportionate to the quantity of B_1.

Phycomyces test.—This method is based on the fact that the growth of the mould *P. blakesleeanus* is proportional to the concentration of B_1 in the medium. It is used in the estimation of B_1 in whole blood, blood plasma, urine and cerebrospinal fluid.

Thiochrome method.—When B_1 is oxidized in an alkaline medium by potassium ferricyanide it is converted quantitatively into thiochrome which is fluorescent under ultraviolet light. The thiochrome can be estimated fluorometrically by comparison with a standard solution.

B_2: Riboflavin (Lactoflavin, Vitamin B_2, Vitamin G).—Riboflavin crystallizes in yellowish brown needles which have no sharp melting point, but darken at 240° C. and decompose at 267–294° C. Solubility in water is very slight, 2·5 parts per thousand at 25° C. It is insoluble in fat solvents. Riboflavin is stable in strongly acid solution, unstable in alkalis, or when exposed to light or irradiation with ultra-violet light. The vitamin is therefore stored in amber-coloured ampoules. Solutions of riboflavin exhibit a strong yellow-green fluorescence which reaches its maximum between pH 6 and 7.

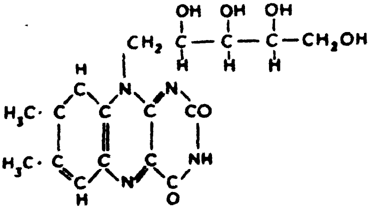
Riboflavin is distributed widely in plants and animals. Amongst the best sources are yeast, milk, white of egg, fish roe, kidney, liver and leafy vegetables. There is not much in grain.

In milk it exists in free form ; in other sources, such as yeast, liver and plants, it is conjugated with other compounds of high molecular weight. The yellow pigment formed by the tubercle bacillus is identical with riboflavin.

Riboflavin is reasonably heat-stable, and is not destroyed unless the medium is alkaline. Appreciable loss occurs in roast and fried foods, but it is only slightly affected by drying or freezing ; canning is much more destructive.

d–Riboflavin is 6 : 7–dimethyl–9–*d*–ribityl–iso–alloxazine.

The formula is :



The Bourquin-Sherman unit is equivalent to 2–2·5 microgrammes of pure riboflavin.

Physiology.—Like B_1, adenylic acid and nicotinic acid, riboflavin is important in metabolism, forming part of a complex enzyme system concerned in the oxidation-reduction reaction of living cells. These enzymes consist of a molecule of which the vitamin is part, combined with a protein molecule. The whole of it exhibits enzymic activity. The enzyme protein combines with flavin phosphoric acid capable of undergoing reversible oxidation and reduction ; this latter forms with a specific protein the yellow oxidation enzyme " flavoprotein " which affects cell respiration. The flavoprotein forms part of a complex oxidation-reduction system for hexose phosphoric acid.

The function of flavoprotein is to aid in the transfer of hydrogen from tissue cells to the blood-stream where free oxygen is available from the breakdown of oxyhæmoglobin and where oxidation of the hydrogen can be accomplished.

Riboflavin not only aids the oxidation of carbohydrates, but also amino acids, lactic acid and aldehydes. It forms part of the co-enzyme of *d*-amino acid oxidase—an enzyme capable of oxidizing many amino-acids.

Most animals, as well as man, are unable to synthesize riboflavin. It must be obtained from diet. Its vitamin activity is due to the fact that, when phosphorylated, it combines with other substances in the cell to form part of enzyme systems. Phosphorylation may occur as soon as it is absorbed from the intestinal wall, since the intestinal mucosa can bring this about in the presence of phosphates. It was originally thought by Laszt and Verzar that the adrenal cortex hormone was essential for phosphorylation, but this is now held to be incorrect.

Riboflavin and nutrition of the eye.—Conjunctivitis and keratitis occur within seven to eight weeks in animals on riboflavin-free diet. These lesions are due to defective metabolism in the lens and cornea. Corneal vascularization is an early and reliable sign of ariboflavinosis, though there is little evidence that riboflavin plays any part in the function of the retina. In man, as described by Kruse and Sydenstricker, there are itching, burning, roughness of the eyelids, lachrymation, photophobia and visual fatigue, and, in China, phlyctenular conjunctivitis. The earliest and commonest sign of ariboflavinosis is circumcorneal injection which may be easily visible or detectable by slit-lamp inspection. It manifests itself as marked congestion and proliferation of the limbic plexus. In 86 per cent. of cases capillaries invade the cornea. In other cases there is gross injection of the fornix and sclera.

The earliest change is marked proliferation and enlargement of the limbic plexus with production of numbers of narrow capillary loops. Mydriasis and disturbances of accommodation may also be noted.

The ocular lesions are cured by riboflavin therapy. The photophobia, burning and itching of the eyes respond within 48 hours to riboflavin in doses of 5–15 mgm. Resolution of the keratitis takes place later.

The relationship of *syphilis* to ariboflavinosis and keratitis is not direct; in the former the keratitis is posterior: in the latter anterior. It is suggested that tropical nutritional amblyopia, or failure of central visual acuity, and essential corneal epithelial dystrophy are also partially due to riboflavin deficiency.

Acne rosacea and associated keratitis are now generally regarded as examples of ariboflavinosis and curable by riboflavin therapy.

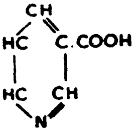
The chief external sign of ariboflavinosis is *cheilosis* (lesions on lips) or pallor of mucosa at the angles of the mouth, followed by maceration, eventually giving rise to transverse fissures extending downwards from the angles of the mouth (Sebrell and Butler). This syndrome of angular stomatitis is identical with that seen in some pellagrins (*see* p. 438) and clears up with daily doses of 3–5 mgm. of riboflavin.

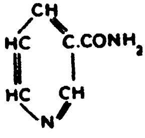
Absorption, storage and excretion.—Riboflavin is absorbed from the intestine and hydrochloric acid is probably needed for this purpose.

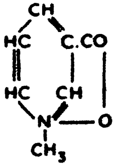
Riboflavin is not phosphorylated or absorbed in patients with certain types of gastro-intestinal disease—such as sprue and cœliac disease—and is only utilized in such patients when injected. The flavin contents of organs does not vary very much. If there is a very considerable increase in intake there is a slight increase in the amount stored in the liver. When adequate, riboflavin is excreted in the urine in the form of uroflavin. Saturation tests with riboflavin have been carried out by Spies and Elvehjem on humans, employing intravenous injections of 200 to 400γ per kilo body weight, but these workers were unable to detect any correlation between the amount of test dose and daily urinary riboflavin excretion.

Human requirements of riboflavin.—These are still conjectural, but it is estimated that boys under six and girls under seven require 450 units daily (0·9–1·2 mgm.); boys from seven to ten and girls from eight to thirteen require 540 units daily (1·08 to 1·32 mgm.); older children and adults require 600 units daily (1·2–2·5 mgm.).

B_3 Nicotinic acid (Niacin).—Nicotinic acid—B-pyridinecarb-oxylic acid— is a member of the B complex. Trigonellin is its methyl betaine and is the form in which it is largely excreted. Its amide—nicotamide—is a component of a complex enzyme system:


Nicotinic Acid


Nicotamide


Trigonellin

Nicotinic acid is a white crystalline solid, melting at 228°-229° C, but soluble in hot water and alcohol. It is one of the most stable of the vitamins and is not oxidized or destroyed in the ordinary process of cooking, exposure to air, light or alkalis. It can be rendered bacteriologically sterile by autoclaving. As an acid it readily forms salts and an amide which are also active. There is no established unit; it was known as a chemical substance long before it was identified as a vitamin.

Distribution and estimation.—Like other members of the vitamin B complex, it is widely distributed in foodstuffs, particularly in meat products, such as liver, eggs and salmon, and also in cereals. White bread contains relatively little compared with wholemeal. The acid is estimated by a colour test with 2: 4-dinitrochlorobenzene, also with cyanogen bromide and aniline. In the blood, nicotinic acid has been estimated quantitatively by its growth-promoting action on various micro-organisms; biologically by its cure of "black tongue" in dogs. In general the nicotinic acid content of most foodstuffs varies from 1 to 100 mgm. per 100 grm. of material, and certain crude liver extracts may contain as much as 200 to 800 mgm. per 100 grm.

Physiology of nicotinic acid.—Nicotinic acid (like riboflavin) forms part of a complex enzyme system capable of undergoing reversible oxidation and reduction. Two substances are essential for fermentation—a heat stable co-enzyme known as cozymase and a heat-labile enzyme, zymase. Cozymase is diphosphopyridine nucleotide (a complex of one molecule of nicotamide, one of adenine, two of ribose, and two of phosphoric acid) and is also known as *co-enzyme I*.

Co-enzyme II contains three molecules of phosphoric acid (triphosphopyridine nucleotide) having a similar structure to co-enzyme I with an additional molecule of phosphoric acid. The most active part of the molecule is the nicotamide component which reversibly takes on hydrogen. Both co-enzyme I and II are widely distributed in tissues, functioning as carriers in numerous oxidation systems including the transfer of hydrogen from metabolites. In uncomplicated nicotinic acid deficiency there is a decrease in the co-enzyme I content of liver and muscle. The content of co-enzyme I and II in the blood can be increased by administration of excessive quantities of nicotinic acid.

It has been asserted that nicotinic acid is associated with porphyrin metabolism, since many manifestations of pellagra, such as diarrhœa and photosensitivity, are often found in patients exhibiting toxic porphyrinuria. It is also claimed that the porphyrin output in pellagra is related to the severity of the skin and mucous membrane lesions, and excretion returns to normal on a yeast and liver diet and with repression of the disease. It is now realised that porphyrinuria is inconstant in pellagra and appears to be of no diagnostic value. For instance, porphyrinuria may decrease in pellagra without nicotinic acid therapy.

It is believed that liver dysfunction, which is nearly always present in pellagrins, may explain the porphyrinuria of pellagra, either in the form of some disturbance in hæmoglobin breakdown with the production of excessive coproporphyrin, or, maybe, the inability of the liver to excrete porphyrin in the bile.

Some indirect evidence exists that riboflavin and nicotinic acid are linked with carbohydrate metabolism, since it has been noted that increase in carbohydrate and insulin dosage in diabetics is often associated with glossitis, cheilosis and stomatitis and, according to Sydenstricker, these symptoms clear up in diabetics after administration of nicotinic acid and riboflavin.

Pellagrins also show hypersensitivity to insulin, so that symptoms of hypoglycæmia rapidly supervene when pellagrins are injected with small quantities of insulin. The injection of 100 mgm. of nicotinic acid into healthy persons and diabetics causes a rise in the blood-sugar level.

It has been suggested that nicotinic acid may play a part in hæmopöiesis, and treatment with nicotinic acid may cause a reticulocyte response in pernicious anæmia. Incidentally, the liver extracts used in the treatment of pernicious anæmia are potent sources of nicotinic acid. It has also been said to have an important function in stimulating gastric secretion and is essential in gastro-intestinal motility. Although nicotinic acid, as essential for human nutrition, must be derived from food, certain animals, such as the rat and sheep, can synthesize it.

Nicotinic acid plays an important part in carbohydrate metabolism of bacteria and is essential for complete utilization of lactic acid.

Pharmacology.—Though overdosage with nicotinic acid produces toxic effects in laboratory animals, none have been observed in man, though the amide is better tolerated. It has been shown that a number of pyridine derivatives allied to nicotinic acid have a similar action in pellagra. Nicotinic acid has a vaso-dilator action which includes flushing of the face and neck, sensation of heat, tingling and itching which come on within seven to ten minutes and last half an hour. There may be slight dizziness, throbbing in the head, headache, sometimes nausea, vomiting and transient abdominal pain, but the blood pressure is not affected. Urticaria, palpitations and cyanosis of the nails have also been described. The vaso-dilator action is checked by glycine in doses of 30 to 60 grm.

Aring and his colleagues showed that nicotinic acid given intravenously increases the rate of intracranial blood flow in humans for 20–60 minutes without any significant change in blood pressure.

Absorption, storage and excretion.—Nicotinic acid is normally absorbed from the intestine, but in gastro-intestinal disease absorption may be defective and occasion signs of nicotinic acid deficiency. Indications are that it is stored in the liver. Pellagrins usually suffer from liver damage. and liver extract is efficient in the treatment of pellagra. Sydenstricker showed that liver extract prepared from a patient dying of pellagra was effective in the treatment of pernicious anæmia, though ineffective in pellagrins. Nicotinic acid is present in the blood and excreted in the urine.

In normal persons the blood level of nicotinic acid ranges from 0·3 to 0·5 mgm. per cent. and the greater part is in the blood corpuscles. Oral administration of 150–300 mgm. of nicotinic acid, or nicotamide, causes a variable transitory rise in the blood level within an hour.

Nicotinic acid is excreted in the urine, partly as such and partly as trigonellin. The average excretion of nicotinic acid as trigonellin amounts to 60 mgm. in twenty-four hours.

Human requirements of nicotinic acid.—The daily requirement of nicotinic acid in adults appears to be 30 to 60 mgm. daily. It has been estimated that the minimal requirements to prevent pellagra in man is 8–16·5 mgm. daily (0·12 to 0·24 mgm. per kg. body weight).

Clinical uses of nicotinic acid.—Nicotinic acid has been used empirically in the treatment of a number of clinical conditions other than frank and subclinical pellagra. Like other vitamins it may act pharmacologically, for instance, in stomato-glossitis (endemic glossitis) in the absence of other signs of pellagra ; in sprue and sprue-like conditions ; in glossitis associated with Vincent's spirochætes, or with leukoplakia. It has also been used in seborrhœic eczema, lupus erythematosus and pruritus vulvæ.

Beneficial results have been claimed in the treatment of psychoses resulting from defective nutrition. Toxic pyschoses, exhaustion delirium and clouding of consciousness may be relieved by nicotinic acid. In some cases very large amounts (400–500 mgm. of nicotinic acid) are necessary to obtain results. The distressing symptoms of Menière's syndrome have been relieved.

As there are certain points of similarity between the symptoms of pellagra and sulphonamide intolerance, it has been claimed that nicotinic acid, 150 mgm. daily, relieves many of the symptoms and decreases the porphyrinuria of patients undergoing sulphonamide therapy.

Vitamin B_6.—Adermin.—This was isolated in 1939 and its structure determined as 2–methyl–3–hydroxyl–4 : 5–dehydroxy-methyl pyridine, or pyroxidin ; like nicotinic acid, it is a pyridine derivative. In doses of 50γ it is effective in the cure of rat dermatitis in about fourteen days. Vitamin B_6 forms colourless crystals with melting point at 200–212° C., soluble in water and alcohol, stable to heat, but not to light. The method of estimation is based on a colour reaction between vitamin B_6, diazotized sulphanilic acid and *p*-nitraniline. Yeast, liver, cereal polishings and pulses are the best sources of vitamin B_6. Vegetables and milk are poor.

Rats fed on diets deficient in B_6 develop cutaneous symptoms characterized by a symmetrical dermatosis affecting first the paws, then the tips of the ears and the nose, which become red, swollen and œdematous. There is said to be a striking similarity between rat acrodynia and chilblains, which suggests that a B_6 deficiency in man may predispose to them. Pigs develop a microcytic hypochromic anæmia curable by B_6. It is essential for the nutrition of the dog, fowl and pigeon and for *Streptococcus hæmolyticus*, *Staphylococcus albus*, yeast, lactic acid bacteria and plants.

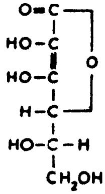
Clinical studies on B_6 have been made on undernourished patients who had clinical evidences of pellagra and beriberi. Intravenous injections of pure synthetic B_6 in 50 mgm. doses were followed by great relief and increased strength. Similarly, large amounts given to pellagrins with macrocytic anæmia and to patients with pernicious anæmia caused the same relief, though the anæmia was not markedly improved. B_6 has also been used in pseudohypertrophic muscular dystrophy, in Parkinsonism, in arsenical peripheral neuritis, and in Sydenham's chorea. It has also been found useful in cheilosis (angular stomatitis) which is usually associated with a riboflavin deficiency. Probably both are essential for the nutrition of the lips at the mucocutaneous junction.

Vitamin C. (Absorbic Acid : Cevitamic Acid)

Vitamin C forms colourless crystals melting at 192° C. It condenses with aldehydes, acetone and other ketones. The reactions of interest and importance are those dealing with oxidation and reduction. When dry and protected from light, vitamin C is stable for a considerable time, even in the tropics. The indicator of efficacy is 2 : 6–dichlorophenolindophenol. In solution, the stability of vitamin C depends on many factors. Autoclaving at 120° C for twenty minutes in oxygen at *p*H 8 results in the loss of 49 per cent. Solutions of vitamin C can be stabilized by the addition of small amounts of fruit acids, such as tartaric or citric acid.

When vitamin C has been reversibly oxidised to dehydro-ascorbic acid by methylene blue it can be reduced by hydrogen sulphide, cysteine and glutathione.

Ascorbic acid has the following formula :



= *l*-Ascorbic acid (vitamin C).

Dehydroascorbic acid is as potent an antiscorbutic as ascorbic acid.

The I.U. is 0·05 mgm. of pure *l*-ascorbic acid. 1 mgm. of vitamin C is therefore equivalent to 20 I.U., but this standard is no longer used.

Distribution.—Vitamin C is present in all living tissues, especially fresh fruits and plants. The richest sources are rose hips and haws, black and red currants, strawberries, cabbages and citrus fruits. Black currants are sometimes as potent as oranges, in which the greater portion is in the peel. For the majority of people the potato is the most important source. Rose hips in Scotland and N. England contain an average of more than 1000 mgm. per 100 grm. of flesh, whilst those from the south contain less. Properly cooked green vegetables are fairly good sources of C. As soon as vegetables or fruit are gathered, an enzyme—ascorbic acid oxidase—is liberated, which slowly oxidizes vitamin C. They should therefore not be kept too long before cooking ; furthermore, 25–60 per cent. may be lost in the cooking water which is rejected. Stewing and baking tend to destroy vitamin C, so that it is doubtful whether vegetable stews in camps and institutions, cooked slowly for very long periods, ever contain vitamin C. Frying definitely destroys it.

There is no appreciable loss in fruit and vegetables kept in cold storage by the " quick-freeze " process. Drying in itself does not affect C. The antiscorbutic value of fruits and vegetables after commercial canning is no less than that of similar foods cooked by household methods.

The C content of cows' milk is very variable. The value drops as soon as the milk is withdrawn and allowed to cool. Commercial evaporated or condensed milk contains no vitamin C, unless added after processing.

Physiology of vitamin C.—C is synthesized by all higher plants and by many animals, except the primates (including man), the guinea-pig and some ungulates. A function that has been well established is the rôle of vitamin C in regulating the colloidal condition of intercellular substance in the animal organism. It was originally shown by Wolbach and others that in the scorbutic animal reticulum and collagen are not formed, but amorphous ground substance and fibroblasts only are present.

Vitamin C is therefore a prerequisite for the formation of inter-cellular material in man.

Teeth and bones.—Vitamin C plays a part in the nutrition of teeth, joints, bones and blood vessels. The changes in the teeth are as follows : changes in the odontoblasts, widening of Tomes' canals in the dentine, in place of which porous bone-like material (osteodentine) is formed. Pulp tissue becomes atrophied and resorbed. These changes commence in the crown and extend to the root. There is no clinical evidence that dental decay in man is due to vitamin deficiency, but bleeding, soreness of gums and loosening of the teeth do appear to be associated with vitamin C deficiency.

The histological changes in the bones of scorbutic animals are commonest at the costochondral junctions, the distal end of the femur, the proximal end of the tibia and the wrist. Bone formation ceases, and the osseous shell becomes rarefied. Formation of cartilage and bone matrices ceases. Vitamin C is necessary for the proper functioning of the osteoblasts. The periosteum becomes stripped from the bone cortex and lack of intercellular material in the blood vessels leads to subperiosteal hæmorrhages. Vitamin C is also essential for the formation of callus in the union of fractured bones.

Wound repair.—Vitamin C is necessary for wound repair and is usually present in young granulation tissue, and adjoining skin.

Hæmopoiësis.—Anæmia is frequently associated with scurvy, and stimulation of the bone marrow is said to follow injection of C. Clinically, many cases of nutritional anæmia have been described which fail to respond to iron, but react to vitamin C, and it is possible that utilization of iron is defective when the store of vitamin C is depleted.

Infection and immunity.—A considerable amount of indirect evidence has been offered for a relationship between vitamin C and infection. Animal experiments tend to show that C has an effect on the production of antibodies. It also possesses bactericidal and bacteriostatic powers and inactivates certain toxins, such as those of *Clostridium œdematiens*, *Bact. dysenteriæ*, and *Clostridium tetani*. Recently it has been suggested that there is close relationship between C in the body and the degree of complement quantities by the leucocytes in the blood, and also some support for the view that it is important in detoxicating processes in the body. Patients showing sensitivity to arsphenamines are said to have low vitamin C levels.

Function of vitamin C in tissues.—It is suggested that C is a component of a reversible oxidation-reduction system acting as a hydrogen transporter or respiratory catalyst. It has been shown, for instance, that *alkaptonuria*, in which homogentisic acid is excreted, turning the urine black, may be produced by administration of amino-acid tyrosine on a diet low in vitamin C. This vitamin is particularly abundant in the corpus luteum, the pituitary, the adrenals and glandular tissue. It is possible that it plays an important part in metabolism of the adrenals and may serve to stabilize the medullary (adrenalin) and the cortical hormones.

It is true that certain symptoms of scurvy resemble those of adrenal insufficiency. There is also a possible relationship between C and function of the thyroid gland. It may be that it antagonizes thyrotoxin.

Carbohydrate metabolism.—When given by the mouth C has no effect on the blood sugar level, but, when given intravenously, the blood sugar drops in a normal individual. From the high C content of active tissues it is considered that it is essential for synthetic processes in the cell.

Absorption and storage.—Vitamin C is selectively absorbed by tissues of the intestinal tract, chiefly by those of the small intestine, and it has long been known that patients suffering from gastro-intestinal diseases excrete subnormal amounts of C in the urine ; there is some evidence that it is inadequately absorbed in patients with achlorhydria.

It is evident that C must be stored in the body, because human scurvy takes several months to develop in diets deficient in this vitamin. It appears to be stored in organs and tissues with high metabolic activity and is present to a great extent in tissues of the young. (The adrenals are the organs richest in C and a considerable amount is present in the lens of the eye). In normal subjects the vitamin C content of the blood plasma ranges from 0·6 to 2·5 mgm. per 100 c.c.

Excretion.—Vitamin C is excreted in the fæces and sweat, but the bulk passes out in the urine, and the rate of excretion depends upon the intake. When administration is continued long enough, the tissues become saturated and a rapid rise in urinary excretion occurs. A daily urinary excretion of 18 mgm. represents the borderline between deficient and adequate intake. Various drugs affect the excretion, especially ammonium chloride. Insulin causes a lowered urinary excretion.

Determination of capillary fragility.—The capillary fragility tests serve as a measure of the physiological indispensable minimum requirement. From simultaneous determinations of capillary fragility tests and blood ascorbic levels it has been found that capillary fragility becomes pathological at blood values between 0·1 and 0·14 mgm. of C per 100 c.c. Blood vitamin C values above 1·4 mgm. per cent. constitute the threshold value and correspond to a state of vitamin C saturation.

Human requirements.—The indispensable minimum is between 25 and 30 mgm. a day—0·4 to 0·5 mgm. per kilo. of bodyweight. The optimum is 50–75 mgm. daily, but more is needed in pregnancy, old age and acute infections.

The fœtus withdraws vitamin C from the mother through the placenta, and the concentration in the blood plasma of the umbilical cord is one and a half to four times as much as that present in the maternal blood at the time of delivery. There is a rapid decrease in vitamin C content during the first few weeks of life, suggesting that vitamin C should be regularly supplied; the content of the breast-fed infant depends on the mother's intake. The requirements of children are greater proportionately than those of adults. The requirement of boys from 13–15 is 90 mgm. daily; that of adults from 30–100 mgm. In women this is naturally increased during pregnancy and lactation. In all infectious conditions the requirement is increased.

Laboratory methods employed for detecting vitamin C deficiency —*Capillary fragility test.* (Rumpel-Leeds test.)—A circular area 60 mm. in diameter is marked off in the antecubital fossa and a blood pressure cuff placed at least 2·5 cm. above this, pumped up to 90 mm. mercury and maintained for fifteen minutes. After the pressure is reduced the number of petechiæ is counted. The test should be carried out at room temperature and the patient should not have had a hot bath on the day of the test or take any exercise within three hours.

The intradermal test.—This depends upon the power of vitamin C in the skin to decolourize the blue dye, 2 : 6—dichlorophenolindophenol, of which 0·1 c.c. of a 1 : 400 dilution is injected into the anterior surface of the forearm. When the individual is saturated the skin is decolourized in less than five minutes; unsaturated individuals require ten minutes or longer.

Urinary excretion.—Some authorities consider that the twenty-four hour excretion of vitamin is reliable for detection of C deficiency. The method of estimation is to determine the amount of urine which has to be added to discharge the colour of a measured quantity of 2 : 6 dichlorophenolindophenol, but it must be remembered that other substances in the urine, such as cysteine and thiosulphates, may also act the same way.

A somewhat similar test has been developed for estimation of vitamin C in the serum.

Clinical uses of vitamin C.—The only disease which specifically responds to vitamin C is scurvy, yet its use has been advocated in the treatment of a number of conditions, such as the zymotic diseases, especially diphtheria. It has also been used in pneumonia, tuberculosis, rheumatism, whooping cough, typhoid, infections of the ear and throat, influenza, malaria, dental and oral conditions, hæmorrhagic diseases, some forms of pernicious anæmia, skin diseases and to an increasing extent in surgery, obstetrics and ophthalmology.

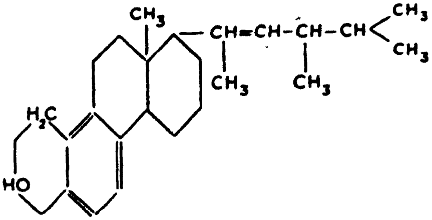
VITAMIN D. (ANTIRACHITIC OR CALCIFYING VITAMIN)

Several substances are antirachitic. The most important are:—

Vitamin D_2 (calciferol). This does not occur naturally, but is manufactured artificially by "activating" ergosterol.

Vitamin D_3, sterol-7-dehydrocholesterol, is the most important naturally-occurring vitamin, being formed in the skin by the action of the sun on the animal. It has the same action as D_2. The chemistry of the sterols is extremely complex. Vitamin D_2 is made by exposing ergosterol to the action of ultra-violet light. The absorption spectrum gives bands of maximum intensity at 260–298μ. Ergosterol is best irradiated in solution, but when alcohol is used it is difficult to avoid over-irradiation. If irradiation is prolonged calciferol is turned into *toxisterol.*

Calciferol has the following formula :



It is a white crystalline substance, melting at 115–117° C. It is stable at room temperature and loses its antirachitic properties at 180° C, but is completely stable dissolved in oil kept at 0° C. Biological assay is the only means available of chemical estimation.

Distribution.—Ergosterol is only found in plants, especially fungi, like ergot from which it derives its name. D_3 is found in egg-yolk, butter and fish oils. Animals gain vitamin D by eating tissues containing it or by direct action of the sun's rays on the provitamin in their own skins. Food *per se* as a source of D is not so important. The formation of vitamin appears to occur *on* the skin. Thus, in birds it takes place in the oil of the preen glands, so that when this is artificially removed they develop rickets. Nothing definite is known on how fish acquire D though it is probable that they are able to synthesize it.

Assimilation.—In birds and animals the vitamin formed on feather or fur is swallowed during preening and licking, but in man it must be absorbed from the skin because irradiation will cure rickets. Bile is essential for its absorption from the intestine, but liquid paraffin or oil hinder, because it is thereby dissolved and excreted in the fæces. It is also possible that it hinders the absorption of calcium and phosphorus.

Storage.—Various tissues store D for different periods : the brain for 1–2 weeks ; the kidneys and liver and blood for 8–12 weeks. Depletion is caused by its excretion into the gut and destruction in the body.

Rachitic diets.—The composition of the diet has a great effect in rickets. The usual diet is one which contains an excess of calcium and acts by forming insoluble phosphates. The bad effect of cereals, especially oatmeal, is well known. This is due to the *phytic acid* of the cereals combining with the calcium of the diet, causing calcium deficiency. The amount of fat in the diet is important as it counteracts the effect of cereals.

Physiology of D.—*Calcification.*—This vitamin regulates the metabolism of calcium and phosphorus, but its mode of action is still obscure. During growth long bones increase in length by calcification of the cartilage between diaphysis and epiphysis. The cartilage is continuously growing on the epiphyseal side, and degenerating on the diaphyseal, which is then invaded by capillaries and osteoblasts. Bone salts are laid down in the degenerating cartilage. In rickets the band of cartilage widens because it keeps on growing, but ceases to degenerate, and no calcification takes place. This results in weakening of the bones, with subsequent bending and fracture. The X-ray picture in severe rickets shows these changes; the end of the diaphysis is smooth, with a clear space between it and the epiphysis. In rickets the end of the diaphysis is uneven and ragged because of the degeneration of the cartilage. The shaft of the bone also shows rarefaction.

When healing commences under the influence of D the first effect is resumption of degeneration of the cartilage cells nearest to the diaphysis, which is rapidly followed by capillary penetration and laying down of bone salts. The rôle of D in calcification of teeth is important.

The amounts of calcium and inorganic phosphorus in the serum are altered; the phosphatase of the blood is raised in rickets and to a lesser degree in osteomalacia. The skeletal muscles and the smooth muscle of the gut lose their tone and the ligaments become lax. Stimulation of growth, as apart from the prevention of rickets, is an important function of vitamin D.

The relation of D to the endocrine glands is important and has a stimulating effect on the parathyroids particularly, and to a lesser extent on the thyroids and pituitary.

The relation to infection is obscure, especially the effect of cod-liver oil on tuberculosis, in which it may possibly exert a specific effect.

Excessive dosage mobilizes the phosphorus and calcium from the body tissues, thus broadly exerting the opposite effect of normal doses. The tubules of the kidney and the media of the larger blood vessels are affected. In the aorta atheromatous changes become evident. The serum phosphorus and calcium are usually grossly raised.

International Unit.—The *I.U.* is the amount of D equal in antirachitic potency to 1 mgm. of the international standard solution, which is equal to 0·025 microgramme (γ) of crystalline D_2 (calciferol).

Estimation.—The "*line test*" is based on the cure of rickets. This is done by feeding identical groups of rats on a rachitic diet until rickets develops. To the diet of one group a standard preparation of D is added. The bone developed during the curative period is stained with silver nitrate and appears as a black line.

***The bone ash method* depends on the prevention of rickets. Groups of rats are fed for four to six weeks with varying levels of the standard preparation being tested. They are then killed and the femoral bones ashed, when comparison of the ash from various groups of animals shows how much calcification has occurred.**

Sources of vitamin D for man.—Sunlight acting directly on the body is the most natural source, but when in excess may cause not only severe sunburn, but fever, malaise and shock. The activated fat is apt to be washed off by bathing.

Artificial sunlight, given by either the carbon arc or mercury vapour quartz lamp, is an excellent substitute for sunlight and has the same effect in prevention and cure of rickets.

***Food.*—The dietetic sources of D in normal foods are dairy produce, fish and dripping. Green vegetables contain none. The value of all dairy produce depends on the diet and exposure to sunlight of hens and cows. Hence eggs contain nearly three times as much D in summer as in winter. Milk is an extremely valuable source, and may be artificially reinforced, either by irradiating the cow or its milk, or by adding D to the cow's diet.**

In concentrated preparations of natural and artificial D it has been shown that 200–500 I.U. given daily as cod-liver oil is sufficient to prevent rickets, while 400–800 I.U. of calciferol is necessary to produce the same effect. There is a risk of hypervitaminosis when excessive doses of calciferol are taken.

Human requirements.—If the diet is not grossly abnormal, especially for calcium and phosphorus, the amounts required at various ages may be stated as follows:

Premature infants	600–800 I.U.
Pregnancy and lactation	600–900 „
Infants	300–600 „
Children at puberty and adolescence	300–600 „
Adults, male and female	300–600 „

In old age the value of sunlight is often lost, so that the diet should be supplemented with cod-liver oil to prevent osteoporosis.

Diseases due to lack of vitamin D.—The commonest is rickets which, contrary to general belief, is still widespread. The rachitic infant develops slowly, is liable to infection and does not attain full stature. Rickets can, however, occur at any age. Infants have been born with rickets, and "late rickets" or "juvenile osteomalacia" may occasionally be found in older children, especially during periods of rapid growth. The clinical picture of rickets is well-known and may be accompanied by pelvic distortion and "greenstick" fractures.

Spasmophilia is due to nervous symptoms of which the underlying factor is a lowered blood calcium. This expresses itself in general irritability, laryngismus stridulus and convulsions.

Other forms of rickets are cœliac rickets, scurvy-rickets, renal rickets and osteomalacia. Osteomalacia of pregnancy, hunger osteomalacia and senile osteoporosis are fundamentally the same, and are due to lack of vitamin D. Tetany is common.

Effect of vitamin D on the teeth.—In rachitic children teeth tend to erupt late and decay early, which appears to be direct effect of lack of this vitamin, but in osteomalacia the teeth do not decay unduly. It therefore appears that vitamin D is not necessary for good teeth in either children or adults, but it is probably valuable in helping to protect them.

Symptoms of vitamin D poisoning.—Loss of appetite follows quickly on the sense of well-being, and then come loss of weight, weariness, weakness and profound mental depression. Death may take place.

Note.—The remaining vitamins —E, K, P— and other less well-defined substances recently described, have been omitted as having little bearing on the subject matter of this book.

CHAPTER XXIV

BERIBERI

Synonyms.—Kakke; Barbiers; Polyneuritis Endemica.

Definition.—Beriberi is a form of multiple peripheral neuritis occurring endemically, or as an epidemic, in most tropical and sub-tropical climates, and also, under certain conditions, in more temperate latitudes. The mortality may be considerable, usually from cardiac failure.

History.—Beriberi was originally described by the early Chinese physicians, and is said to be referred to in the Neiching, a medical work attributed to Hwangti (B.C. 2697). The special nature of beriberi was recognized by the Dutch in their early years in the East. Later, it was studied by British physicians in India, particularly by Malcomsen, Carter, Waring, and Morehead. It was not until an epidemic in Brazil that beriberi began to receive attention from a later generation of medical men; and only when Anderson, Simmons, Scheube and Baelz took up the subject in Japan was it studied by modern methods, accurately defined, and its true pathology apprehended. Scheube and Baelz were the first to show distinctly that beriberi is a peripheral neuritis simulating that of diphtheria and of alcohol—a view subsequently confirmed and adopted by Pekelharing and Winkler, and by most subsequent observers. Mainly owing to the investigations of Eijkman, Grijns (1901), Braddon, Cooper, Fraser, Stanton, Funk, Vedder, Hopkins, Hausette, Chick and Margaret Hume, its principal—it may not be the only—ætiological factor has been shown to be a dietary of which the staple ingredient is overmilled rice or other cereal which has been deprived of vitamin B_1.

Geographical distribution.—The area of the endemic distribution of beriberi is co-extensive, probably, with the tropical and subtropical belts. It was formerly the scourge of many of the mines and plantations of the Malay and Eastern Archipelago. It was apt to break out among the coolie gangs engaged on extensive engineering works in the tropics, such as the Panama Canal or the Congo Railway. It haunted the Dutch army in Sumatra, used to be common enough in the British armies in India and was the scourge of the Japanese navy. It is still found in many parts of Japan, particularly in her large, low-lying, damp, overcrowded cities. It occurs in China, the Philippines, the Eastern Peninsula, India, and Africa. We have had accounts of a small epidemic among a group of Western Australian natives, and also among Chinese on the eastern seaboard of Australia, a continent where beriberi was formerly supposed not to exist. Many years ago beriberi broke out in a lunatic asylum in Dublin; and apparently the same disease has been seen in similar institutions in the United States and in France, and also among the Newfoundland fishermen and those on the North American coast. Tomasson reported (1933) an epidemic in the Westman Islands, Iceland. The diet consisted of fresh fish which, even in large quantities, is deficient in vitamin B_1. Elshout and Lentjes described a similar outbreak amongst prisoners on an island off Holland.

Epidemiology and endemiology.—*Sex, age, occupation.*—Beriberi attacks both sexes. It is not uncommon in the breast-fed infants of beriberic mothers. This form, called *infantile beriberi*, may declare itself in varying ways.

Ship beriberi.—Beriberi is prevalent among the native crews, more rarely, though occasionally, among the European officers and sailors, of ships on the high

From 1894 up to 1920, or thereabouts, the disease was common in European crews of Swedish and Norwegian ships, which are in far better sanitary condition than British ships, and yet beriberi is comparatively rare in the latter. The modern explanation is that, since the year named, the crews of the Norwegian mercantile marine have been provided, under the terms of a statute, with bread baked from white flour, or a mixture of wheat and rye, so that their diet is inadequate in vitamins. Ship beriberi holds a place intermediate between true beriberi and scurvy, and is closely related to the disease found among the Rand miners of South Africa. A similar disease has recently been noted amongst the whale fishers of South Georgia. In Newfoundland beriberi of both forms is found at times when the diet is reduced to a regime of bread and molasses (Aykroyd). A number of cases have been reported from H.M. ships in the Persian Gulf.

Asylum beriberi.—The Dublin lunatic asylum, built for 1,000 inmates, had 1,500 inmates crowded into it when beriberi broke out, due to dietetic causes.

Ætiology.—The earliest investigators of beriberi believed that it was a degenerative multiple neuritis indistinguishable from that produced by alcohol or diphtheria, and that it was due to an infection or intoxication, and much effort was directed to the discovery of the poison. All these theories are now a matter of history, for they have been replaced by the vitamin-deficiency theory.

History.—Lunin (1881) found that mice could not survive on artificially composed milk. Socin (1891) and Pekelharing (1905) postulated some substance necessary for nutrition. Eijkman (1890) and later Grijns proved the existence of a food deficiency in beriberi. Braddon (1907), later Fraser and Stanton established the correctness of these observations in man in Malaya, and Hopkins in England devised experiments directed to the recognition of food constituents necessary for growth. Funk (1911), in attempting to isolate the principle from rice-polishings, coined the word *vitamin*. The water-soluble vitamin was found essential for growth by McCollum and Davis (1915) The isolation of the principle was made possible by the work of Sidell (1916), Kimersley and Peters (1924), and finally the isolation of vitamin B_1 was effected by Jansen and Donath (1926). The chemical constitution was established by Windaus *et al* (1932), Williams *et al* (1935), the synthesis by Williams (1936), Bergel and Todd (1936), Andersag and Westphal (1936).

Thanks to this pioneer work, we know that the beriberi of the Eastern Peninsula, of the Eastern Archipelago, of the Philippines, of China and of Japan, is a sequel of a diet in which overmilled rice is the principal element, that is, rice from which the entire pericarp and germ have been removed; and that in this pericarp and germ there is a substance essential to the proper nutrition of the nervous system of man and of many other warm-blooded vertebrates.

If a fowl or pigeon be fed exclusively on "*paddi*," that is, rice from which the husk has not been removed, it will thrive and very likely gain weight; but if it be fed exclusively on a diet of white rice and grain, that is, rice from which the pericarp has been completely removed, after a short time it will show signs of peripheral neuritis, lose weight and, if the exclusive diet be persisted in, die with all the signs of a multiple peripheral neuritis. This *polyneuritis gallinarum* (or *p. columbarum*)—as it is called—is evidently the result of the deprivation of some element of food essential for the proper nutrition of the nervous system of the bird, and the element is located in the pericarp and germ of the rice grain (Figs. 56, 57). Almost miraculous recoveries in the stricken birds take place after hypodermic injection of an extract of the germ centre of wheat or other cereal.

The greater part of the rice grain is starch, and covering the central starch core there is a thin aleurone layer containing the proteid and fat constituents of the grain. Externally there is an adherent layer, the pericarp, which varies in colour from red to white according to the variety of the rice. The pericarp contains the salts. The grain itself is covered by a husk, which is discarded as chaff.

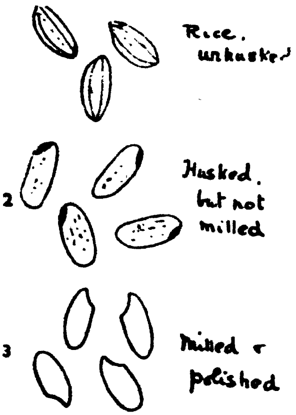


Fig. 56. — Showing the various stages in milling the rice grain. 1, Rice grain in the natural condition enclosed in the husk or enclosing glumes; 2, After removal of the husk, but retaining the pericarp or "silver-skin" and the embryo; 3, After milling and polishing; both "silver-skin" and embryo are removed and the grains are "polished" by rubbing with talc between sheepskins. (*After Chick and Hume, "Trans. Soc. Trop. Med. and Hyg."*)

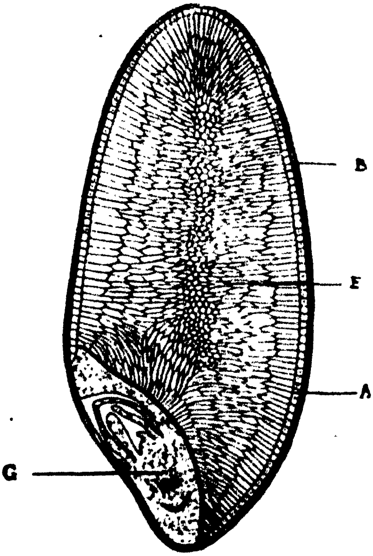


Fig. 57.—Diagram of longitudinal section through a grain of wheat showing (a) aleurone layer of cells forming the outermost layer of the endosperm, removed with the pericarp during milling; (b) pericarp forming the branny envelope; (e) parenchymatous cells of the endosperm; (g) embryo or germ. (*By permission of H. M. Stationery Office, from Dr. J. M. Hamill's "Report on the Value of Bread made from Different Varieties of Wheat."*)

Conditions under which rice is grown.—Rice grows normally in puddled fields in which a layer of water is allowed to remain until the grain is almost ready for reaping, and this puddled rice has a nutritional value of approximately one-third less than the same rice grown under dry rain-fed conditions; it contains also a lower content of vitamin B_1; the Chinese eat mostly polished rice, normally [illegible] from fresh vegetables, shortage of which has from time to time led to a great increase of beriberi in Malaya. (*See also* Chap. II, p. 29.)

Fraser and Stanton showed—and their observations have been abundantly confirmed—that the antineuritic element is located in the pericarp of the rice grain, in the aleurone layer, and in the embryo of the grain, that it is soluble in water and alcohol, is stable in acid but unstable in alkaline solutions, is thermolabile—being destroyed by a temperature of 130° C.—and that it is dialysable; that it is not a phytin or a fat, and that, although itself not containing phosphorus, the amount in any given rice is a reliable indication of the safety, or otherwise, of that rice as a staple article of food. Rice containing less than 0·4 per cent. of P_2O_5 they considered unsafe, and believed that its persistent use may lead to beriberi.

The polyneuritis of the fowl is identical clinically and ætiologically with the polyneuritis, called beriberi, occurring in man. For, as has been both accidentally and intentionally done, if the same experiment with rice-feeding be tried on man the result is identical—beriberi is induced. Thus, following the lines of the earlier experiments of Fletcher, Fraser, and Stanton, Strong and Crowell conducted a series of experiments on twenty-four life-sentenced prisoners, and were able to prove (*a*) the non-communicability of the disease, and (*b*) its production in man solely by means of diet. A similar condition has been produced in rats.

Acting on these findings, the governments of Singapore and the Federated Malay States forbade the use of white or polished rice in their jails, lunatic asylums, schools and hospitals, with the result that beriberi, which until then had been the cause of an enormous mortality and morbidity, has been practically banished. Corresponding results have accrued from the same practice in Dutch East Indies, the Philippines, and elsewhere. In India decorticated rice is practically the staple diet of many millions, though beriberi is endemic only in a few circumscribed areas in Bengal and Assam, the north-east coast of Madras, the coast of Burma, and certain river valleys. The basal factor in India must be a fundamentally poor diet, whether of rice or other food grains. The period of development of beriberi in man was determined by Fraser and Stanton as between eighty and ninety days. The part that vitamin B_1* plays in beriberi is now becoming clearer. Walshe (1941) claimed that, both clinically and pathologically, beriberi is a typical polyneuritis, differing in no essential from other varieties. The nervous signs and symptoms are those of a multiple symmetrical nervous lesion, the cardiac manifestations those of polyneuritis.

It is, however, clear that deprivation of B_1 alone is not sufficient to cause beriberi in fowls or man, for patients dying of anorexia nervosa do not develop polyneuritis. The significance of B_1 is in relation to carbohydrate metabolism, rather than to its direct effect on the nervous system. Human and avian nervous systems can be deprived of B_1 with impunity when no carbohydrates are given. B_1 acts as a catalyst in carbohydrate metabolism of the nerve cell and heart muscle. In the absence of B_1, cellular carbohydrate metabolism breaks down at the stage of pyruvic-acid formation. This substance accumulates in the cells, where its presence can be detected. It is, however, an error to suppose that pyruvic acid is toxic. Peters and his colleagues believe that B_1 functions as a co-enzyme in the metabolism of carbohydrates and plays a part in the oxidation breakdown of pyruvic acid. Therefore accumulation of this acid or of pyruvates in the blood and central nervous system, and its excess in the urine, is related to the deficiency of B_1. It is therefore essential for normal growth and the maintenance of body weight.

---

* An account of the chemistry, physiology and pharmacology is given on p. 400.

Incidence.—The incidence of beriberi is greatest in those regions where polished rice and refined cereals form the bulk of the diet. It constitutes one of the most potent causes of mortality in Japanese infants. From 1920–1929 there was an average of 17,000 deaths from this cause in Japan. Berberi appeared in the beleaguered troops at the siege of Kut in 1916. Balfour stated that every pregnant woman in S. India suffers from it. In S. China beriberi is common in the later months of pregnancy and in the puerperium.

In people living on an inadequate diet the raised basal metabolic rate resulting from fever increases the liability to beriberi—as after smallpox, cholera or meningitis. In China, for instance, 10 per cent. of patients show some reflex abnormality suggesting latent beriberi. Thus, any lowering of the general resistance leads to the development of polyneuritis. Breast-fed babies born of mothers suffering from the disease are themselves liable to it.

Pathology.—The post-mortem appearances of beriberi resemble the accepted descriptions of peripheral neuritis. There is a degeneration of the peripheral nerves—more especially of their distal ends—and there is secondary atrophic degeneration of muscle, including that of the heart. Degenerative nerve-changes may be detected in the nerve-centres and throughout the implicated neurones, as in other forms of peripheral neuritis. There is invariably an involvement of the vagus, with degenerative changes in its root in the floor of the fourth ventricle. Microscopically, the nerve-trucks show changes, from a slight medullary degeneration to complete destruction of the nerve (Wallerian degeneration). Regenerative processes occur side by side with the degenerative (Fig. 58). As a rule, some fibres in the vagus and sympathetic escape; thus, the cardiac branches in the heart-muscle and the bronchial and œsophageal twigs are usually unaffected. According to Vedder, the membranes of the spinal cord are often congested and œdematous; scattered fibres in all tracts show the same kind of changes as the peripheral nerves. Degenerative changes are also found in the anterior and posterior horn cells, as well as in the sympathetic ganglia. If there is anything peculiar about the post-mortem appearances in beriberi, it arises from the somewhat special implication of the central and peripheral organs of the circulation—namely, dilatation of the heart, especially of the right side, and great accumulation of blood in the right heart and in the veins. In addition, there is a marked liability in many cases to serous effusion into the pericardium, pleural cavities, peritoneum, and cellular tissue. This very marked liability to serous effusion and the tendency to cardiac dilatation may be said to be more or less distinctive of beriberi as compared with other forms of multiple neuritis. Œdema of the cardiac muscle naturally interferes with the normal fluid exchange within the fibres and therefore with its contractibility. According to Mebius, when vitamin B_1 is deficient, full muscular contractibility is impossible owing to water absorption (hydropic degeneration of Wenckebach). The average weight of the Japanese heart in beriberi is 368 grm. (normal 300 grm.). The enlargement is particularly noticeable on the right side, especially the right auricle, and the walls are paper-thin. Without doubt, water-retention in beriberi is of the greatest importance in elucidating the mechanism of symptom production. Œdema of the lungs also is not uncommon, and has, probably, a pathology similar to that of the connective-tissue œdema. There is no nephritis, but pressure congestion of the liver (nutmeg liver). Duodenitis is frequent.

The general affection of the whole nervous system, involving the central and peripheral structures, is identical with the found in diphtheritic or alcoholic neuritis.

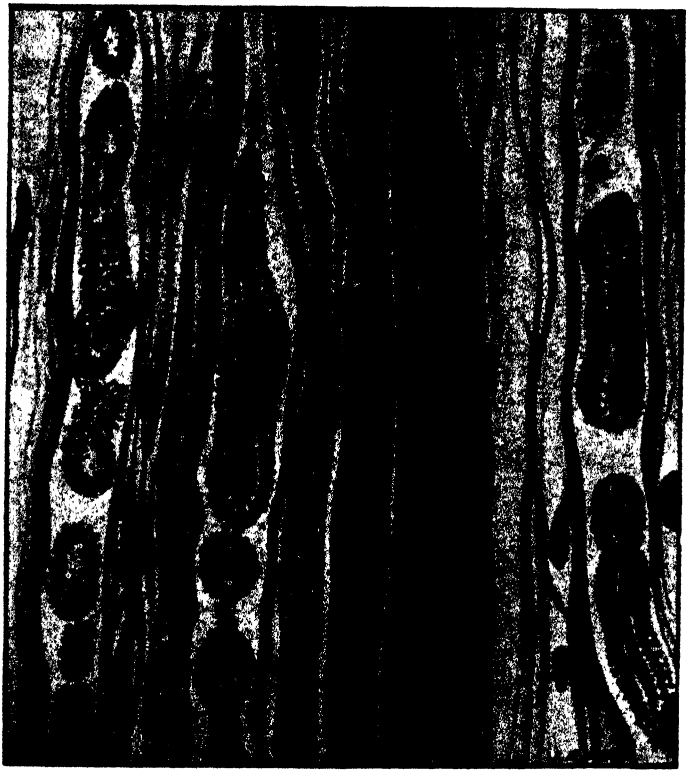


Fig. 58.—Longitudinal section of external popliteal nerve in beriberi.

One medullated fibre in centre is practically intact; the others show typical fragmentation of myelin sheath with swelling of remains of nerve-fibre.

(*From a preparation by Dr. A. C. Stevenson.*)

Symptoms. *Primary Beriberi* (*Naturally-occurring disease*).—Beriberi assumes varying clinical forms according to the extent and position of the nervous lesions. It is insidious in onset, but it may occasionally be ushered in by acute symptoms ending fatally within a few hours without development of any symptoms referable to the nervous system. As a general rule, it is classified into two main forms, according as the peripheral nerves or the cardiovascular system are most affected. The former is known as paraplegic or " dry " berberi, the latter as œdematous or " wet " beriberi. It must be understood that in all its forms beriberi is the same disease, and that a clinical classification has but a conventional value. Sudden death from heart failure may ensue, especially in œdematous cases.

Paraplegic beriberi (Fig. 59).—There is a certain amount of anæsthesia or numbness of the skin, particularly over the front of the tibiæ, the dorsa of the feet, the sides of the thighs, perhaps also of the finger-tips, and one or two areas on the arms and the trunk. Deep sensibility (Abadie's sign), elicited by compression of the Achilles tendon, is usually numbed or entirely lost. The calves may be strikingly thin and the gastrocnemii flabby, and if they and the neighbouring muscles are handled somewhat roughly, particularly if they are squeezed against the underlying bones, the patient will call out in pain and try to drag the limb away. Toe and foot-drop can frequently be demonstrated. Weakness spreads upwards, first involving the extensor muscles of the leg, and then the extensors and flexors of the thigh. The skin of the limbs becomes shiny. The thenar, hypothenar, plantar and arm muscles, like the calf muscles, may be wasted and flabby and exhibit fibrillary twitchings. Very probably there is a loss of fat, the panniculus adiposus being everywhere meagre. If tested electrically, the

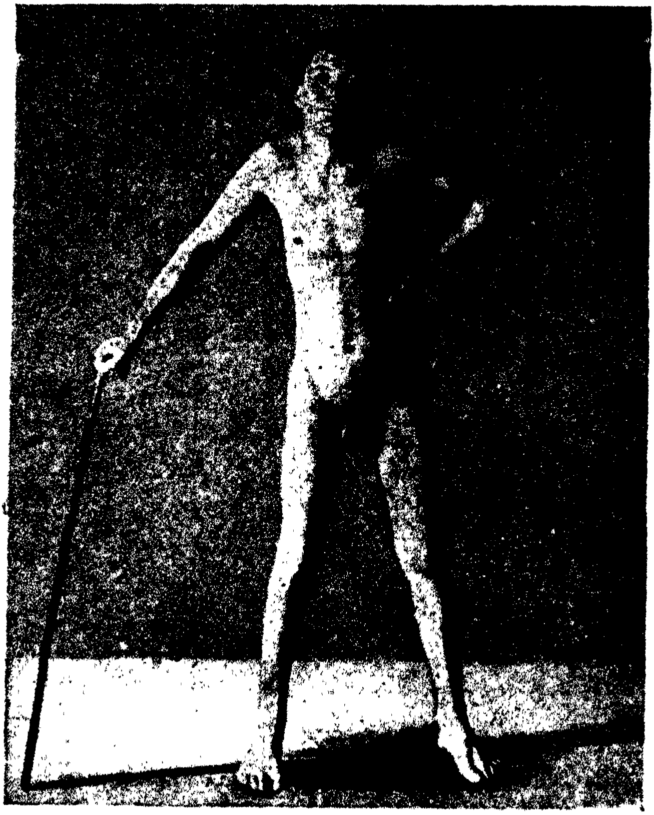


Fig. 59.—Ataxic or paraplegic beriberi, showing characteristic attitude.

muscles exhibit the reaction of degeneration. If the knee reflex be tested in the usual way, it is at first increased, but after the first week there will be no response whatever ; nor can any clonus be elicited, but occasionally a reflex contraction of the hamstrings may take place, giving a false impression of a knee-jerk. As a rule, all the deep reflexes are lost ; but the superficial, unless in extreme paresis and muscular atrophy, are usually present and more or less active. If, in severe cases, the patient is set to button his jacket or to pick up a pin, possibly he has a difficulty about it, or perhaps he cannot ; he may bungle and fumble like the advanced ataxic. The fibres of the affected muscles, when struck with a patellar hammer, often contract locally in a particularly painful manner known as myœdema. There may be wrist drop (Fig. 60).

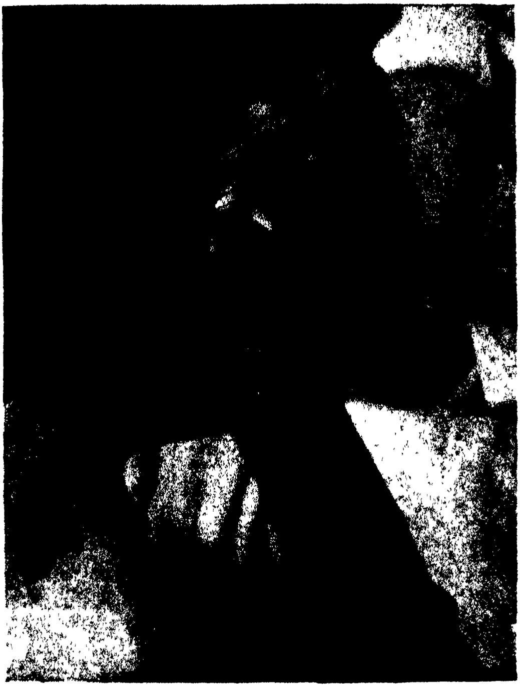


Fig. 60.—Paraplegic beriberi, showing wasting of extensor muscles and wrist-drop.

There is more than ataxia, however, for the hand-grasp is so enfeebled that the patient may have a difficulty in holding his rice-bowl as well as in feeding himself. There is no tremor of the hands ; and never, or very rarely, is there any paresis of the ocular muscles, or of the muscles of the face, of mastication, of the tongue, or of the pharynx. The sphincters and bladder operate satisfactorily, and the functions of the alimentary canal are carried on fairly well, although there is often some dyspeptic distension and oppression after food. If the patient can walk at all, his gait will be markedly ataxic; but, in addition to want of co-ordinating power, there is great muscular weakness. If he is laid on the bed and asked to raise his legs, he is perhaps hardly able to get them off the mat, to cross them, or to place one foot on top of the other. Very probably he is the subject of marked foot-drop, so that he drags his toes when he attempts, in walking, to advance the foot; he has therefore to raise the foot very high, letting it fall on the ground with a flop when he brings it down again (steppage gait). His ataxia and his muscular weakness, as well as the partial anæsthesia from which he suffers, force him to adopt a variety of devices to assist him in progression. Although mental symptoms are uncommon, defects of memory often occur. Lesions of the optic nerve have been described, and include concentric contraction of the field of vision, temporal pallor of the disc and retrobulbar neuritis.

61.—Œdematous beriberi with paresis of legs in Gold Coast native boy (*Dr. S. A. Mac'*

The general health is good, for the most part; the tongue is clean, the bowels are fairly regular, there is no fever. Loss of sphincteric control does not occur until very late. Digestion, assimilation, and excretion are satisfactory.

Cardiac beriberi, wet beriberi.—Instead of being wasted, as in paraplegic cases, the face is puffy and heavy; the lips possibly slightly cyanosed; and the arms, hands, trunk, legs, and feet are distended with œdema (Fig. 61). It may be thought at first from the œdema that it is a case of nation of the scanty, dark-coloured urine shows that it is of high specific gravity and contains no albumin, or only a mere trace. Careful observation will discover that the œdema is somewhat firmer than that of nephritis and, in not a few instances, that it does not involve the scrotum. Occasionally it is peculiarly localized and fugitive. A bruit and other evidences of dilatation of the heart are discovered.

Occasionally irregularity may be associated with slowing of the heart-beat, and heart-block may occur in such cases. The liver is frequently swollen and tender. The lungs may (or may not) present signs of single or double hydrothorax, but they themselves are healthy. The patient can hardly walk—partly from breathlessness, partly on account of mechanical interference by the dropsy with the movements of the legs, partly, perhaps, from some degree of paresis. He may have ankle-drop ; if firm pressure be brought to bear on the calf-muscles through the œdema, signs of hyperæsthesia of the muscles may or may not be elicited. Knee-jerks are generally absent, and there is numbness of the shins and finger-tips. The tongue is clean, the appetite fair, and there is no fever. But there may be præcordial distress and even pain, and, as this is aggravated by a full meal, the patient eats sparingly. The amount of urine is generally very much reduced—even to a few ounces.

In this patient, therefore, there are the same signs of peripheral neuritis and of dilatation of the heart as in the other cases. In addition, there is a somewhat firm œdema, which is not altogether cardiac, but, as its character and the circumstances in which it is found suggest, is probably connected with the play of transudation and absorption in the connective tissues.

When the heart is examined, if the case be at all recent or moderately severe, the impulse is diffuse ; there is epigastric pulsation ; the carotids throb too violently ; and there is that peculiar wobbling, pulsating movement in the jugulars that denotes tricuspid insufficiency. " Pistol shot " sounds are heard on auscultation over the larger arteries. On percussion the præcordial area is frequently enlarged, perhaps very greatly enlarged, especially to the right ; and on auscultation loud bruits, usually systolic in rhythm, may be heard. Marked reduplication of the sounds, particularly of the second, is noted. The auscultator may be impressed, in a large proportion of cases, by the peculiar spacing of the intervals between the sounds. It may be hardly possible to tell by the ear alone which is the first pause and which is the second. They seem alike in point of duration (tic-tac rhythm) ; so that the sounds resemble the beats of a well-hung pendulum clock, evenly spaced, and not, as they are in health, separated by a long and a short interval. It will also be observed that the heart is very irritable, easily quickened by exertion. In addition to peripheral neuritis, there is serious disease in the circulatory system, particularly in its innervation ; there is dilatation of the right side of the heart, and a state of relaxed arterial tension. Paralysis of the left recurrent laryngeal nerve by a grossly distended right auricle has been recorded. There is a wide range in the pulse-pressure, and Aalsmeer and Richter have shown that there is almost invariably a low diastolic blood-pressure which can be influenced by the injection of adrenalin (the adrenalin effect). Pitressin raises the diastolic pressure from almost zero to 75 mm. and the venous pressure falls ; this beneficial effect may last 1¾ hours.

Usually in well marked cases, the electrocardiagram shows distinct changes of low voltage and an indefinite inverted or flattened T wave in I, II and III leads, shrinking of the P—R interval and prolongation of the Q—T interval.

The cardiac enlargement in human beriberi was ascribed by Aalsmeer and

Wenckebach to œdema of the heart-muscle, which results in an interference with its contractile power without disturbance of its excitability.

Wenckebach investigated a number of cases of cardiac beriberi in the Dutch East Indies and Singapore, taking special precautions to inject hardening fluid, and he was thereby able to confirm the presence of certain gross anatomical changes which are demonstrable during life by radiography. The whole of the right side of the heart is enlarged, while the left remains comparatively small; the conus arteriosus takes part in the change. The large systemic veins are commonly dilated, and as much as three litres of blood may escape from the right auricle. The extrapericardial pulmonary vessels are not abnormally congested. Microscopic examination of the heart muscle after death reveal intracellular œdema, sarcolysis, and hydropic degeneration, probably primarily due to excess of lactic acid, brought about by defective oxygenation. The primary lesion is, therefore, a loss of contractibility of the heart muscle, related to water retention, with consequent loss of peripheral vascular tone. The clinical picture and its response to adrenalin and pitressin, together with the lowering of diastolic pressure, accord with these findings.

Aalsmeer employed the results of these observations as a practical test to indicate the stage of the disease and response to treatment. The diastolic pressure is known as the " minimum tone pressure," because it is the pressure registered by the sphygmomanometer at the moment when the auscultatory bruit disappears with decompression of the brachial artery. The essence of the test is that, when the diastolic pressure is registered, the administration of adrenalin in hypodermic doses of 1 mgm. will be found, if observations are taken at five-minute intervals, to bring the pressure down to zero in an uncured case of beriberi. That is to say, the auscultatory murmur will persist during complete relaxation of the pressure of the artery as long as the patient is under the influence of adrenalin.

Cardiac attacks.—Most cases die from paresis and over-distension of the right heart, complicated and aggravated by œdema of the lungs, diaphragmatic paralysis, hydrothorax or hydropericardium. Sudden cardiac failure (termed by the Japanese " Shôshin ") is often contributed to by the co-existence of pleural effusion, hydropericardium, paresis of the diaphragm, over-distension of the stomach by food or gas, and, above all, by œdema of the lungs. It can readily be understood how any additional obstruction of this description would still further tax the dilated, enfeebled heart and determine the fatal issue.

Great variety in degree and combination of symptoms.—Some cases are so trifling that the patients are up and moving about with more or less freedom; others lie like logs in their beds, unable to move a limb or perhaps even a finger. Some are atrophied to skeletons, others are swollen out with dropsy, and some show just sufficient dropsy to conceal the atrophy of muscles. Though the cranial nerves above the seventh are very rarely involved, in some the laryngeal muscles are paralysed, the patient being unable to speak above a whisper or to produce an explosive cough. In one or two cases the abdominal and the perineal muscles may be so profoundly paralysed that, when cough is attempted, at most a husky expiration is produced, while the belly is bulged forward and the perineum shot downward by the sudden contraction of the muscles of expiration. The deep reflexes do not reappear for months, perhaps, after the patient is well in all other respects. In some epidemic outbreaks, as, for instance, in Iraq in 1916, an irregular *pyrexia*, seldom exceeding 100° F., was noted.

Uncertain course.—Beriberi slowly or rapidly declares itself after an incubation period of weeks or months; it may be preceded by a period of intermitting languor, aching legs, palpitations, breathlessness, slowly advancing œdema of legs or face; or the patient may wake up some morning and find that during the night he has become dropsical or paretic. Thus, the disease may develop slowly or rapidly. Equally uncertain are its progress and danger; within a day or a week, or at any time during its course, it may assume fulminating malignant characters. It may completely subside in a few days, or it may drag on for months. It may get well apparently and then relapse. It may, and generally does, clear up completely; or it may leave a dilated heart, or atrophied limb muscles with corresponding deformity. The variety in the severity, progress and duration of beriberi is infinite; but in all cases the essential symptoms are the same—greater or less œdema, especially over the shins; muscular feebleness and hyperæsthesia, especially of the legs; numbness, especially of the front of the shins, of the finger-tips, occasionally of the lips; liability to palpitation from cardiac dilatation, and to sudden death from the same cause.

Secondary beriberi. *Beriberi manifestations produced by other diseases. Alcoholic beriberi.*—It has long been recognized that alcoholic neuritis resembles in many respects the paraplegic form of beriberi. It resembles it so closely that in recent years the idea has gained ground that this resemblance is more than fortuitous, and that in both conditions there is an antecedent deficiency of vitamin B_1. The theoretical considerations advanced by Shattuck have led to the recognition of a variety of intestinal conditions in which polyneuritis may occur, such as gastric carcinoma, chronic intestinal obstruction, and ulcerative colitis, and, in the opinion of some observers, all these should be included under the heading of secondary beriberi. Cases have been reported of alcoholic addicts with congestive heart failure and polyneuritis who have recovered completely after treatment by rest, a high-calorie diet, and vitamin B_1.

Multiple factors are probably concerned in the production of alcoholic beriberi, including defects in diet and assimilation acting in conjunction with increased tissue requirements for vitamin B_1 due to an increased rate or type of metabolism. Many cases of alcoholic neuritis have now been cured by the continued injection of aneurin. Weiss and Wilkins (1936) described the clinical syndrome of cardiac beriberi associated with alcoholic gastritis, which resembles the classical form of the disease. Alcohol is a significant factor in precipitating beriberi, not only because it supplies calories without B_1, but also because its metabolic effect is similar to that of pure carbohydrate. In response to aneurin the cardiovascular disorders disappear before the polyneuritis. Dysfunction of the cardiovascular system resulting from unbalanced food intake is a disease of regular occurrence in America. Tachycardia, followed by bradycardia, and gallop rhythm with electrocardiographic changes are considered to be characteristic of the beriberic heart.

Strauss thought that the *polyneuritis of pregnancy* may be of the same nature when pernicious vomiting occurs. In *diabetic neuritis* also it has been shown that the injection of aneurin exerts an influence upon carbohydrate metabolism.

Infantile beriberi.—This form is common in Egypt, the Philippine Islands, South China and certain Pacific Islands, and causes a high infantile death-rate. In the Philippines especially it was a terrible scourge, accounting for 16,500 deaths annually, or 28·1 per cent. of total deaths in infants under one year. It is not necessary to regard it as resembling adult beriberi in miniature, for it differs in many essentials. The disease often occurs in the rainy season. It is never seen in Caucasians, rarely in half-castes, and should be regarded as strikingly a disease of poverty. It usually affects breast-fed infants of mothers who are either themselves victims of the disease or subsist on a diet poor in vitamins. In Hong Kong Fehily stated that in initial, subacute and acute infantile beriberi breast-feeding immediately antedates the symptoms, but in the chronic form breast-feeding might have ceased weeks or even months previously. Removing the infant from the breast, or administering an extract of rice bran, usually leads to a rapid cure.

Vedder and his American colleagues believed that the disease depends upon deficiency during uterine life and after birth of a substance in the milk which is essential to the growth and development of the child's nervous system. However, in children who die in this manner no imperfection or lack of development of the nervous system has been noted. In the most acute type it is children previously healthy, 1½ to 3 months old, who are usually attacked; after a series of convulsions the child suddenly dies of acute heart-failure. In less fulminating cases, vomiting, dyspnœa, dysphagia, and aphonia may precede heart-failure. The child moans in characteristic fashion and the beriberic cry is diagnostic. Ptosis is also common. The blood pressure is low. The total acidity and free hydrochloric acid in the gastric juice are reduced. Occasionally, chronic cases are seen in which progressive weakness and wasting, with periodical attacks of vomiting, occur. In neither form has true paralysis been noted, except that underlying aphonia which was ascribed by Japanese workers to a paralysis of the left recurrent laryngeal nerve from pressure by a dilated left auricle. According to Chan, the knee-jerks are usually absent.

Some highly interesting suggestions were made by G. W. Bray on the inhabitants of Nauru in the Pacific. The death-rate from infantile beriberi in that island, amongst breast-fed babies from eight to ten weeks after birth, had been approximately 30 per cent. of the total deaths during twelve years. The mothers themselves showed no signs of dietetic deficiency, though their dietary was singularly deficient in vitamin B_1. Bray was able to demonstrate the almost instantaneous effects of partially-fermented "toddy" (the sap of the coco-nut spathe), not only in cure, but also in prevention. The dosage of "toddy" is half a drachm twice daily during the first month, one drachm twice daily during the second, three times daily from three to six months, and over that age, three to four ounces weekly. In consequence of this simple measure the disease ceased to exist amongst the Nauruans, while the incidence of a variety of other disorders, such as bronchitis, pneumonia, furunculosis and otitis media abated. It appeared that this peculiarly dramatic form of infantile beriberi became prevalent since the use of "toddy" was prohibited by Government order.

The therapeutic action of the toddy yeast in restoring these children is as rapid and dramatic as are similar extracts in artificially-produced polyneuritis of fowls and pigeons.

In the acute type of the disease, gastro-enteric, pneumonic and meningitic signs and symptoms prevail. There is at first disclination for food, followed by extreme restlessness, increased epigastric swellings, paroxysmal crying and general anasarca. Vomiting is the first sign of impending death. Dyspnœa and cyanosis supervene and the child dies in convulsions (Fig. 62). The temperature is slightly raised to about 100° F.

The diagnosis of infantile beriberi is greatly aided by blood examination : a lymphopenia is almost invariably noticed, with a total absence of small lymphocytes. Bray was able to show that the therapeutic action of vitamin B_1 is greatly enhanced by the synergic influence of vitamin A, as in cod-liver oil.

Fig. 62.—Infantile beriberi. Nauruan child in convulsions. Note general anasarca. (*Dr. G. W. Bray.*)

Mortality.—The mortality in beriberi varies in different epidemics and in different localities. On the whole, it is greater in low than in high latitudes, in the dropsical than in the atrophic forms, in the acute than in the chronic. In some epidemics it is as high as 30 per cent. of those attacked ; in others as low as 6 per cent., or even lower.

Burning Feet.—" Chachaleh " (Somaliland) ; " Bárasheh."

This is a very chronic condition which has been recognized in Malaya, British Guiana, West Africa, and Somaliland for many years. Buchanan reported on a series of over 100 cases from Somaliland. Pain is usually generalized, but may occur in various localities, particularly the joints, and at the back of the neck and in the shoulders.

In 82 per cent. there was solid œdema of varying degree, whilst there was thickening of the subcutaneous tissues, especially of the thighs, abdomen, and pectoral and deltoid areas in 41 per cent. Epigastric pain is common and constipation the rule. The knee-jerks are diminished in 39 per cent. of cases. In Malaya, Kingsbury noted sixteen cases, all, with one exception, in Southern Indians. The patients complain of severe " burning feet," usually limited to the soles, but occasionally involving the lower part of the legs. In some instances the pain was definitely worse in the mornings and was always intensified by walking. Sometimes there is a definite history of formication. This condition is now considered to be a deficiency disease, probably connected with beriberi, and also to be curable by administration of vitamin B_1. Since Moore, Scott, Landor and Pallister have described neurological symptoms (weakness, ataxia, incoordination and loss of visual and auditory acuity) associated with burning feet, Stannus believes that it is a further manifestation of ariboflavinosis (p. 441).

Diagnosis.—Usually the diagnosis of beriberi is not difficult. Multiple peripheral neuritis occurring as an epidemic, or in a place or ship in which the disease has occurred on some previous occasion may, as a rule, be set down as beriberi. Sporadic cases may be difficult to diagnose, especially if there is a history of alcoholism, of malaria or of drugging with arsenic. The presence, actual or past, of œdema—especially of œdema over the shins—and palpitations and other evidences of cardiac implication, are significant of beriberi. In the atrophic or paralytic type the *jongck* or "*squatting test*" is very useful. The patient is unable to assume, or rise from, a squatting position with his hands on top of his head. It must be borne in mind that slight anæsthesia of the prætibial skin area, slight œdema of the same region, slight hyperæsthesia of the calf muscles, and, perhaps, impairment or absence of knee-jerk may be the only signs. *Rheumatism is rare in the tropics.*

Pyruvic acid determination in the blood is of diagnostic value. In acute beriberi the blood contains about 2 mgm. per cent.; in untreated chronic cases 1·5 mgm. per cent. and in those injected with aneurin about 0·5 mgm.

Meyers introduced two new tests for the diagnosis of beriberi. The first is the development of, or increase in, an audible sound in the ante-cubital space after subcutaneous injection of adrenalin. The second and more important is the estimation of diuresis after the fasting patient has drunk a litre of water. The volume of urine passed every half hour is charted for four hours. A normal person excretes all the fluid, but in beriberi there is water retention; this should disappear after treatment with aneurin. (Volhard's diuresis test.)

Differential diagnosis.—Cases have been diagnosed as cardiac disease, tabes dorsalis, muscular rheumatism, progressive muscular atrophy, ascending spinal paralysis, and have over and over again been relegated to that refuge for ignorance, malaria. There should be no difficulty in distinguishing beriberi from tabes dorsalis, by the Argyll-Robertson pupil and the positive Wassermann reaction. In both paraplegic beriberi and locomotor ataxia, Abadie's sign (absence of pain on compressing the tendo Achillis) is present.

Beriberi can be differentiated from *alcoholic neuritis* by the tremors and mental disturbances which are generally obvious; from *arsenical neuritis* by the pigmentation, the diarrhœa, and digestive disturbances, and by the hyperkeratosis of the palms and feet that is apt to occur in this intoxication; from *chronic lead-poisoning* by the blue line on the gums, the wasting of the arm and leg muscles which are most in use, the characteristic sparing of the supinator longus, and the basophilic stippling of the red blood-corpuscles; from *lathyrism* by the presence of the knee-jerks and the absence of muscular hyperæsthesia in this affection; and from triorthocresyl phosphate poisoning (ginger or jake paralysis) which causes a flaccid form of motor paralysis. The differential diagnosis from heart disease, chronic nephritis, and ancylostomiasis is sufficiently obvious.

It may be necessary to differentiate Korsakoff's syndrome, Landry's paralysis or Wernicke's syndrome.

Schretzenmayr described the radiographic appearances of the beriberi heart. Three stages can be distinguished; of these the second, with special enlargement of the right auricle, is regarded as characteristic of beriberi.

There are probably other forms of polyneuritis distinct from beriberi, which may closely simulate it. Possibly these infectious forms of polyneuritis are occasioned by an organism as yet undetermined. Possibly also, infective forms of polyneuritis occur in association with food-deficiency. These may account for sporadic cases in which pyrexia is prominent, and also for isolated outbreaks not apparently associated with a faulty dietary.

Famine œdema (nutritional œdema) is more pronounced than œdema of simple starvation, and other causes than mere lack of sufficient nutriment are at work. It is most pronounced in the feet and legs, and marked muscular weakness and alimentary-tract disturbance are common. When there was a shortage of fats, as in Central Europe during the 1914-1918 war, ocular manifestations were frequent. In Java and Haiti a form of malnutritional œdema is prevalent among individuals whose diet is inadequate, and amongst infants fed on a preponderantly starchy diet over a long period. In these a generalized dropsy, similar to famine œdema and œdematous beriberi, is observed. Though resembling œdematous beriberi, this condition is probably not due to vitamin deficiency, but to lack of albumin and fats in the food. Blood analysis reveals a deficency in the albumin-content. The condition is curable by a liberal dietary.

Prognosis.—The tendency to dilatation of the heart is the dangerous element in beriberi; it should always dominate treatment. It is wonderful how rapidly it may come on, and how quickly it may prove fatal. Sudden deaths, occurring sometimes from syncope—from instantaneous failure, as well as from the somewhat slower process of increasing over-distension—are constantly found. An absolutely favourable prognosis, therefore, ought never to be ventured, even in the mildest-looking case, nor so long as the patient is exposed to the conditions causing the disease, or the neuritis appears to be active. That is a lesson which is often, and sometimes painfully, borne in upon the practitioner in beriberi districts.

Evidences of grave heart-implication, such as pulsating cervical vessels, equal spacing of the intervals between the sounds audible on auscultation, enlargement of cardiac dullness, especially to the right, epigastric pulsation, a rapid feeble pulse, a distended stomach, cold extremities, cyanosis, dyspnœa, and a disproportion in the strength of the heart- and wrist-beats, are significant of danger. *Paralysis of the diaphragm, of the intercostal muscles, extensive serous effusions and very scanty urine* are also unfavourable signs.

Vomiting.—No one can say when or how soon fatal implication of the cardiac nerves and muscle may take place, but vomiting is always an ugly and threatening symptom. The Japanese regard it as of fatal import. Marked dilatation of the stomach has a similar significance.

Prognosis is improved if the patient is placed on a non-beriberic diet and is treated with full doses of aneurin before the heart-muscle or the cardiac or respiratory nerves are gravely degenerated.

TREATMENT

The first and most important thing is the diet. From this, rice, especially white rice, should be eliminated, and some article rich in vitamins—such as beans, peas, peanuts, barley, wheaten flour (not overmilled), or oatmeal —substituted. Apart from other considerations, rice is a bad food for beriberics ; it is too bulky. Eggs are valuable sources of the anti-beriberi factor, which is not destroyed even when they are dried. Yeast has curative properties ; the extract known as *marmite* may be given in doses of 1·5 grm. daily. Animal food, including fat and milk, must enter into the dietary for general nutritional purposes. The worst cases, particularly if there is any sign of serious cardiac implication, should remain in bed : but the mild cases had better spend the greater part of the day in the open air.

In cardiac cases, with a view to diminishing to some extent the bulk of blood in the vessels and heart, the seriously affected patients should take little fluid, and keep the bowels free by full and repeated doses of some saline aperient. Small doses of digitalis or strophanthus seem to do good. Should signs of acute cardiac distress appear, full doses—3, 4, or 5 drops of the 1 per cent. solution—of nitroglycerin are indicated, and intravenous injections of ouabäine (a French preparation of strophanthin) $\frac{1}{250}$ to $\frac{1}{60}$ gr. may be given. The dose must be repeated every quarter- or half-hour, and kept up until the threatening symptoms pass away. In suddenly developed cardiac attacks, inhalations of nitrite of amyl, pending the operation of nitroglycerin, are useful. Should signs of cardiac distension and failure persist and increase in spite of these means, there must be no hesitation in bleeding the patient, taking, if it will flow, eight or ten ounces from the arm or (this failing for any reason) from the external jugular. Often, as the blood flows, rapid amelioration of the alarming condition sets in, and the patient is, for the time being, tided over an acute danger and given another chance. The bleeding should be repeated if the alarming symptoms recur, as they are almost sure to do. Oxygen inhalations, if available, are worth trying in cardiac attacks. Pleural and pericardial effusions should be sought, and, if deemed to be interfering in the slightest degree with the circulation or respiration, drawn off with the aspirator.

The introduction of vitamin B_1 (aneurin) as a therapeutic agent has entirely revolutionized the treatment of beriberi, and its dramatic effects are best observed in the acute cardiac cases when given in big doses. Hawes, Monteiro and Smith emphasize that it is in the acute attacks which break out without any previous warning that its effects are best seen. Wilkinson recommends immediate intravenous injection of 50 mgm. of aneurin, to be repeated two or three times in twenty-four hours until serial skiagrams show that the heart has become reduced to normal limits. In moribund patients the injection has been made direct into the jugular vein with spectacular success. There are two crystalline preparations in use for injection, *Betaxan* (Bayer) and *Benerva* (Hoffman, La Roche). These preparations normally contain 2 mgm., but the strong or " forte " dose is 10 mgm., of crystalline aneurin per c.c.

preparation "Bemax" is widely used. *Crystovibex* (Parke, Davis & Co.) is aneurin in tablet form, and is issued in two strengths, 333 international units (1 mgm.) or 2,231·2 international units (6·7 mgm.). Benerva and Betaxan are also issued in tablet form for oral administration in doses of 1 mgm. each.

Hawes originally showed that active extracts of vitamin B_1, when given by the mouth, are destroyed in the stomach, but after the injection of a potent extract most striking therapeutic effects are noted. In cardiac or œdematous cases the patient, even when moribund, at first becomes restless after the injection, but no effect is noted in the pulse rate or in the diastolic or systolic pressures for an hour or more. If insufficient vitamin B_1 has been injected, there may be a return of the dyspnœa, sudden collapse and death. In many cases, recovery is extremely dramatic. The dosage varies in different cases. The reaction is quantitative, and the results become apparent in the rise of systolic and diastolic blood-pressures.

In advanced paraplegic cases the results of aneurin treatment are by no means so satisfactory; whereas pain and subjective dysæsthesia are relieved, the nervous signs take a long time to disappear. In the Far East, especially in China, results are disappointing, because patients inevitably relapse when they return home and resume their polished rice dietary.

Breast-fed beriberic infants should be removed from the mother and handed over to a healthy wet-nurse, or placed on the bottle. Sometimes this is impracticable; in such cases in the Philippines a preparation of extract of rice-polishings, known as "tiqui-tiqui," has the reputation of being wonderfully efficacious. It is given to the extent of 5 c.c. a day in 20-drop doses every two hours. At the end of twenty-four hours the most alarming symptoms disappear, and the child is well in three days. If the case is a very severe one, double doses should be given, and the tiqui-tiqui continued so long as there is any aphonia. Under modern conditions obviously aneurin is indicated. How found that in the most acute cases one injection of 5 mgm. aneurin, followed by 3 mgm. by mouth, sufficed. In chronic cases oral administration is satisfactory.

Excretion of aneurin.—The excretion of aneurin in the urine can be estimated, with sufficient accuracy to be of clinical value, by the thiochrome method without the use of the fluorimeter. Rapid excretion takes place in the first three hours after subcutaneous or intramuscular injection. It is suggested that a certain amount of injected aneurin is excreted before there is time for it to be stored in the tissues (Marrack and Hoellering).

Other measures.—For the atrophy of the muscles and anæsthesia of the skin, faradization and massage should be employed as soon as the muscular hyperæsthesia has begun to subside. Hot-air baths are of considerable service. Care should be taken that permanent deformity does not occur from contraction of muscles. Foot-drop should be counteracted by Phelps's talipes splint with an elastic accumulator, and any other threatened deformity appropriately met. Relapses must not be risked by a return to the original diet.

Prophylaxis.—In institutions under Government control, or in conditions in which it can be successfully enforced, there should be a stringent rule against the use of overmilled rice. To legislate against the use of white rice in countries in which rice is the staple food would not be politic, and could only lead to opposition and defeat the object in view ; but the authorities, by educative methods and in other ways, can do much to eradicate gradually any prejudices there may be among the natives against undermilled rice. The committee on beriberi control of the Far Eastern Association of Tropical Medicine (1925) urged upon governments that, wherever overmilled rice forms a staple diet, steps should be taken to discourage the use of rice from which essential food factors have been removed ; that safe storage should be provided for undermilled rice ; and that the use of accessory foods should be encouraged.

It is most important that a practical test should be elaborated for rice which may cause beriberi when used as a staple article of diet.

As a prophylactic, *marmite*, in small ¼-oz. cubes, may be taken twice a week. Military and other expeditions should be warned that tinned meats are notably deficient in antineuritic vitamins and require the addition of other foodstuffs to protect against beriberi as well as scurvy. Dried eggs are especially valuable, but are too expensive to be used on any extensive scale.

Contrary to the conditions in scurvy, the human body does not appear to possess any appreciable reserve store of the antineuritic vitamin upon which to draw in a dietetic emergency. A constant supply, therefore, of the substance must always be maintained. The moral of this is, that for the prevention of beriberi for any population living on a restricted diet, such as soldiers and sailors on active service on land and sea, the germ and bran of wheat should be included in the manufacture of bread or biscuit where the rest of the ration consists of tinned or otherwise preserved foods. Diets which contain large proportions of starch and sugar should be supplemented by foods containing ample quantities of vitamin B_1. Where maize is the staple article of diet the meal should include the germ.

CHAPTER XXV

PELLAGRA

Synonyms.—Mal de la Rosa; Mal Rosso; Alpine Scurvy; Asturian Rose.

Definition and description.—An endemic disease of slow evolution, which is undoubtedly connected with dietetic deficiencies, characterized by a complexity of nervous, alimentary and cutaneous symptoms, which make their first appearance during the spring months (sometimes the autumn), and recur year after year at the same season, remitting more or less during the winter months. It is for the most part confined to the poorer classes, especially agricultural labourers. The more distinctive features are (*a*) a remitting dermatitis of the exposed parts of the body; (*b*) marked emaciation; (*c*) profound depression alternating with mania; (*d*) a terminal confusional insanity.

History.—The history of pellagra is comparatively recent. In Spain it was first described by Casal in 1763, under the name of *mal de la rosa*. In Italy the disease, under the name of *Scorbuto alpino*, was described by Odoardi in 1776 and by Frapolli in 1771. The earliest mention of pellagra in France dates from 1829. We know nothing of the history of pellagra in Egypt before the publication of Pruner's "Topographie médicale du Caire," in 1847. In the United States of America, although there is evidence of its sporadic occurrence there for at least fifty years, before its nature was recognized, pellagra was first diagnosed as such in 1907. It is especially prevalent in the South-Eastern States. Dr. H. F. Harris, Health Officer of the Georgia State Board of Health, estimated that there were 50,000 cases of pellagra in his State, and in 1916 there were 150,000 pellagrins in the Southern United States alone, though during recent years the American outbreak has become milder.

Since 1912 sporadic cases of the disease have been reported in the British Isles. Many of these fall into the category of what is known as "secondary pellagra."[1]

Geographical distribution.—*Europe*: Pellagra is found in Northern Portugal, in Spain, in Italy, in the south-west of France, sparingly in Denmark and in the British Isles, in the Austrian Tyrol, in Hungary, Croatia, Dalmatia, Bosnia, Jugoslavia, Bulgaria, Turkey, Greece, Corfu, Roumania, Bessarabia, Kherson, Poland and Transcaucasia. A few cases have been reported from Germany. *Africa*: Algeria, Tunis, Egypt, Sudan, the Red Sea coast, Rhodesia, Nyasaland, and among the Kaffirs and Zulus. It has also been recognized in Tanganyika, Kenya and on the Gold Coast. *Asia*: It has been reported from Asia Minor, Armenia, Syria, North Behar and Deccan in India, the Malay States, the Philippine Islands, Japan, China and Korea. An outbreak of pellagra was recorded in Nanking in 1920, in Shanghai in 1940, and by French observers in Szechuan. Yu reported typical cases in Manchuria. It was especially prevalent among Turkish troops and Armenian refugees in Palestine and Syria during the 1914-18 war. *America*: Canada (since 1914), the United States, Mexico,

---

[1] For more detailed information the reader is referred to the masterly summary by H. S. Stannus in the *Tropical Diseases Bulletin*, **33**, 10–12, and **34**, 3.

Central America, Brazil, the Argentine, Barbados, Jamaica, and probably other West India Islands. *Australasia:* Pellagra has been reported from New Caledonia and in Australia (Melbourne).

Pellagra in Great Britain.—According to Stannus, the first authentic case in Great Britain was reported by Howden in 1866, the second by Brown in 1906, and the third by Brown and Low from Shetland in 1909. In 1912 a series of six cases was investigated by Sambon and Chalmers, and in 1913 Box published his two famous cases in St. Thomas' Hospital. Since then it has come to be generally recognized that pellagra is found sporadically in lunatic asylums and other institutions, in subjects of general malnutrition. In the statistics of the Board of Control in the period 1913–1918, 45 deaths were noted. In 1922 there were 21 deaths, mostly from the Lancashire Mental Hospital, Rainhill, and during the period 1913–1928 there were 104 deaths from pellagra amongst asylum inmates.

Epidemiology and endemiology.—An important epidemiological feature of pellagra is the marked fluctuation of its prevalence from year to year. Thus, there may be long periods of quiescence, followed by years of considerable activity during which the disease may be looked upon as a new invasion. There is no evidence that pellagra is spread by contagion. The sound may associate with the sick and remain healthy. Doctors, nurses, and attendants on pellagrins are not known to contract the disease. Pellagrous wet-nurses do not infect their charges.

Associated diseases, such as ancylostomiasis, bilharziasis, malaria, tuberculosis, cœliac disease, idiopathic steatorrhœa, sprue, chronic bacillary dysentery and syphilis, play a very important part in favouring the development of pellagra, in accelerating its course, in modifying and aggravating its symptoms, and in determining its mode of termination.

Season.—Of all diseases with marked seasonal connection, pellagra is one of the most striking. The pellagra season varies in different localities, but is always the same in the same locality.

In Europe the disease invariably appears in manifest and epidemic form during the spring and autumn quarters, the spring outbreaks being by far the more severe, the autumnal recurrence often inconspicuous or lacking. In Egypt, according to Chalmers, there is a spring invasion in April and May, and an autumn recurrence in November. In Nyasaland, according to Stannus, pellagra seems to prevail chiefly during August, September, and October, which are the spring months in the southern hemisphere, and again, though to a lesser extent, in January, February, and March (fall recurrence). In the United States of America, owing to the vast extent of territory and great variety of climates, the periodical incidence of the disease is necessarily different in different sections. In the Northern States, as in Europe, the disease exhibits the usual well-marked double incidence, the spring outbreak occurring in May and June, the autumnal one in September and October. In the far south the disease may appear as early as January, and may be met at any period of the year. In Barbados it seems to prevail more or less from May to October or November. While the wide range of pellagra throughout the world might suggest that climate exerts no special influence, the very definite seasonal periodicity shows that climatic factors play an important, though indirect, part.

Sex.—Both sexes are liable, but in different places the disease exhibits a very different predilection for the one or other sex in accordance with the occupations and habits of the people. In the United States it is said to be more prevalent in women from 17 to 40 years of age; the debilitating effects of menstruation, pregnancy, and lactation are held to be predisposing and determining factors.

Age.—Pellagra is a disease of middle age, the majority of cases occurring between twenty and fifty. Within the endemic centres children are attacked, and infantile pellagra is common in West and East Africa and Southern China (*see* p. 441).

Occupation.—The disease prevails most of all among field-labourers. The inhabitants of towns, even of those in the very heart of intensely pellagrous districts, usually enjoy immunity. Although it has been stated that pellagra is rare in the Jewish race, it is quite common in Palestine, where it is confined to the poor town dwellers, whilst agricultural labourers for the most part escape.

The flooding of some of the Southern States in America by the overflowing of the Mississippi in 1927 afforded a practical example of the dietary factor. Pellagra, though common in these States, depends to a great extent on economic conditions. The diet of molasses and cornmeal contains very little of the PP factor, and only when the financial conditions allow can milk, eggs, etc., be purchased. The failure of the cotton crop meant poverty, reduced food, and pellagra.

Ætiology.—Pellagra was formerly ascribed to the most varied causes, such as insolation, poverty, insanitary dwellings, syphilis, irritant oils, bad weather, alcohol, garlic, onions, maize. Some regarded it as "sunstroke of the skin." "Sun disease" was an old popular name, and certainly the skin manifestations of pellagra are influenced by the action of the direct rays of the sun: This was proved experimentally, first by Gherardini, who varied the limits of the eruption by systematically displacing parts of the clothing; and later by Hameau, who obtained differently shaped patches of erythema by means of gloves fenestrated in different ways. In smallpox, and also in other exanthemata, light has a decided influence, more particularly the actinic rays, on the production of skin eruptions. Although light may influence the eruption in pellagra, this is no adequate reason for concluding that insolation is the cause of the disease, any more than that it is the cause of smallpox, and in fact other stimuli applied to the skin, such as pressure or exposure to X-rays, may cause the appearance of a pellágrous dermatitis.

Pellagra and maize.—The general opinion was that pellagra appeared soon after the introduction of maize into Europe, and that it advanced *pari passu* with the extension of maize cultivation and with the more general adoption of the new cereal as an article of food. For these and other reasons maize was held by many to be the causative agent of pellagra, just as a certain condition of rye was known to be the cause of ergotism; and, as in the latter case, various theories have been propounded to explain the operation of the assumed cause.

Lombroso and Bellardini, in 1871, first advanced the theory that the prevalence of pellagra in Italy was due to the consumption of diseased maize, and their ideas subsequently formed the basis for public measures against the disease in that country, as well as in Southern Europe. In Lower Egypt, as pointed out by Wilson, pellagra is common, as compared to Upper Egypt, and it is in the Delta that the proportion of land given over to maize is considerably higher than that under wheat, so the distribution of pellagra in that country corresponds to the area of maize cultivation.

Deeks in 1912, and Funk in the same year, suggested that pellagra was a disease produced by a deficiency in diet. In 1914 Goldberger and Wheeler fed a squad of eleven prisoners on a rich carbohydrate diet deficient in proteins. After five months, six developed cutaneous symptoms suggestive of pellagra (the first lesions consisted of an erythematous patch on the scrotum). An experiment in the converse direction also proved successful, for, by substituting a rich protein diet for one consisting in great part of carbohydrates, they succeeded in banishing pellagra from an orphanage asylum in which up to that time pellagra had been in evidence. In 1917 Goldberger successfully disposed of the "infection theory" by obtaining sixteen volunteers who attempted to infect themselves by ingesting skin scales and naso-pharyngeal secretions of pellagrins over a period of six months. They remained quite healthy. In 1919 the commission which investigated the prevalence of pellagra amongst the Turkish prisoners in Egypt attributed the cause to a primary deficiency of "biological proteins" (B.P.V. = Biological protein value).

The Vitamin B_2 Complex.—Goldberger, who at first believed that an amino-acid deficiency was the cause of pellagra, in 1922 obtained evidence pointing in another direction. Having discovered that yeast was effective in preventing and curing blacktongue in dogs, generally considered to be analogous to pellagra, Goldberger and Tanner tried the effect of yeast as a prophylactic in the human disease, and found that 30 grm. daily of brewers' yeast gave complete protection. This would supply less than 15 grm. protein, and later it was found that an acid preparation of yeast, which contained very little protein-nitrogen, in doses of 15 grm. daily, was equally effective. A PP (pellagra-preventive) factor was therefore postulated in yeast and other foodstuffs. As the result of these investigations on man and experimental work on rats, Goldberger and his colleagues were able to identify the PP factor with a vitamin in the yeast-vitamin complex differing from aneurin in its stability to heat and its distribution in foodstuffs.

It was subsequently discovered that the PP factor was in fact composed of elements of the vitamin B complex the chief constituent of which was nicotinic acid or nicotinamide. Modern opinion is that riboflavin (the typical vitamin B_2) is concerned in the genesis of several of the more prominent pellagrous lesions. "Ariboflavinosis" is quite distinctive and has been well described by Sydenstricker.

Liver and meat contain a high proportion of nicotinic acid and this explains the well-ascertained fact that these substances are effective in the treatment of pellagra in man, as well as of blacktongue in dogs. Nicotinic acid and riboflavin have been found to be efficacious in the treatment of pellagra (*see* p. 443).

Although there can be no doubt that deficiency of nicotinic acid causes pellagra, the relation of the disease to the amount of this vitamin in food and the association of pellagra with maize is not yet quite clear. Maize contains less nicotinic acid (1–1·6 mgm. per 100 grm.) than wheat (4 mgm.), but more than rye, millet and refined flour. It is possible that the nicotinic acid in maize is, in some ways, unavailable.

The not infrequent occurrence of *secondary pellagra* is probably due to non-absorption of the necessary vitamins by a diseased or non-functioning mucosa.

Pathology.—The pathological features essential to pellagra may be obscured by complicating diseases, such as bacillary dysentery and tuberculosis. The morbid anatomy is neither constant nor characteristic; for this the chronicity of the disease, the variety of the symptoms, and the many intercurrent affections which may arise are responsible.

A constant and striking feature is the great emaciation. The viscera show chronic degenerative changes, particularly fatty degeneration, and a characteristic deep pigmentation. The intestinal walls are greatly attenuated through wasting

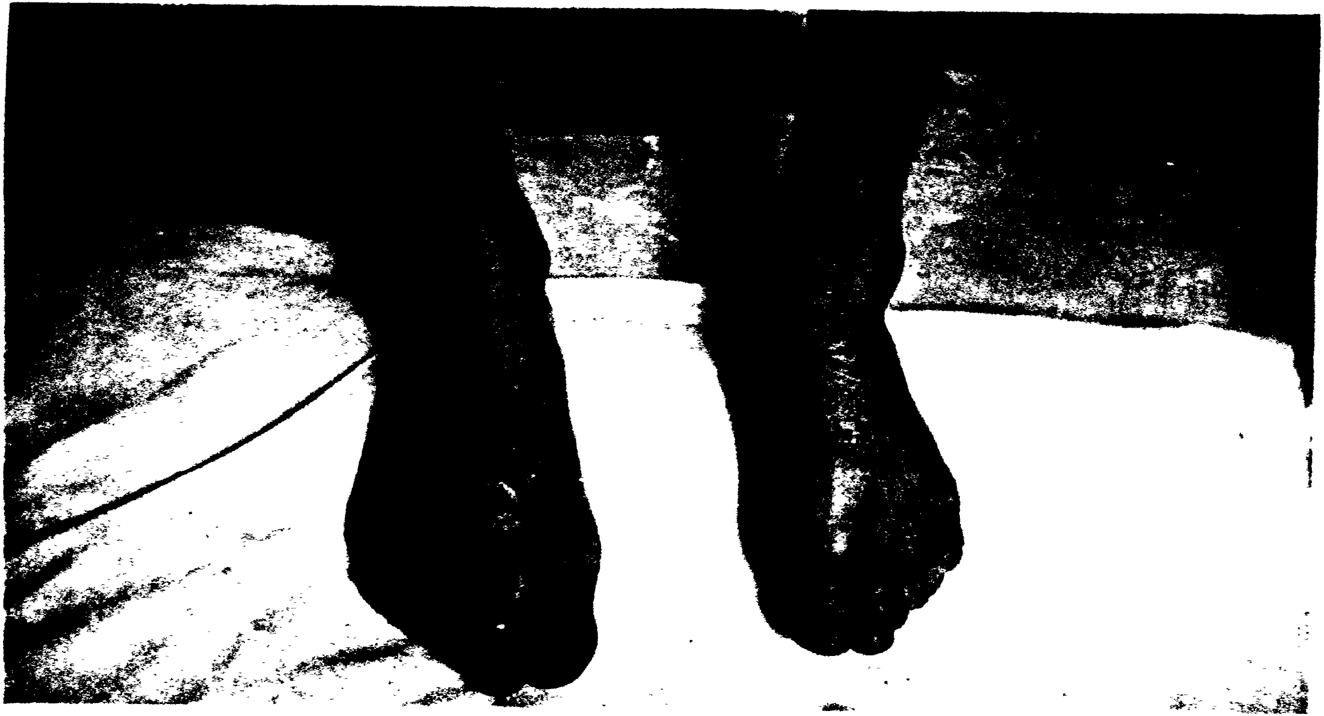


Photo: Dr. A. D. Bigland.

PELLAGRA RASH ON FEET.

Dorsa of feet had been exposed to sun in area between turned-up trousers and uppers of shoes.

Plate VIII

of their muscular coat, while at the same time the mucous lining is hyperæmic and, not infrequently, ulcerated. The liver and spleen are usually atrophied. The suprarenal capsules may be atrophied and the cortex may be black, while the medulla is whitish and may be the seat of hæmorrhages. The heart is usually in a condition of brown atrophy and weighs only 2–3 ounces.

There may be wasting of the brain, the ventricles being distended by an excess of fluid. In the cord the lateral columns and the crossed pyramidal tract are especially implicated, but the direct cerebellar tracts usually escape. The interior cornual cells are frequently atrophied and deeply pigmented. The posterior columns do not escape, the median portion often being degenerated. The degenerative changes in the lateral columns are chiefly in the middle and lower thirds of the dorsal region, those of the posterior columns principally in the cervical and upper dorsal region. The cerebro-spinal fluid shows little change; there is usually no increase in the globulins.

Mott remarked on the changes in the cerebrum, cerebellum, pons, medulla, and spinal cord that in none of the sections is there any evidence of meningeal or perivascular infiltration with lymphocytes, plasma cells, or polymorphonuclear leucocytes. All the changes were like those produced by a chronic toxæmia, possibly in the manner already suggested. The posterior spinal ganglia cells show, in varying degree, a pronounced chromatolysis, swelling of cells, and disappearance of Nissl's granules, and all the anterior-horn cells and their homologues in the medulla and pons a varying degree of perinuclear chromatolysis. With the Marchi method, degeneration is most definite in the column of Goll. In most cases the afferent tracts are more affected than the efferent. There is usually marked chromatolysis of the cells of Clarke's columns. The Betz cells of the cortex and the cells of Purkinje showed similar changes, but in a lesser degree. In short, the changes in the central nervous system resemble those of central neuritis (Adolf Meyer) or of subacute combined degeneration of the cord.

Shattuck drew attention to the close ætiological relationship between beriberi, Korsakoff's syndrome, pellagra, central neuritis, and subacute combined degeneration of the cord.

Central neuritis, which is undoubtedly allied to pellagra, was first described by H. H. Scott on sugar estates in Jamaica, and it was subsequently found in Sierra Leone and Nigeria. The central nervous lesions are widespread; the peripheral nerves are demyelinated and the posterior root ganglia of the spinal cord show degenerative changes. The medulla, cerebellum, basal ganglia and optic nerves are also affected.

Clinical pathology.—There is hypochlorhydria in 40 per cent., and quite frequently achlorhydria. In advanced pellagra there is usually anæmia, which is of macrocytic and hyperchromic type in about 50 per cent.: microcytic in the other half. The total leucocyte count is not disturbed, though there is often lymphocytosis. An indirect van den Bergh reaction is usually present in the serum. There is no change in the corpuscular fragility; the plasma albumin is diminished.

The fæces are pale, foul, milky, soapy, sometimes steatorrhœic. The urine is generally alkaline and may rapidly become ammoniacal. It may also contain tube-casts, traces of albumin and, usually, indican. Much attention has recently been drawn to the excretion of coproporphyrin (porphyrinuria) and speculations have been made regarding its significance. Some regard it as indicating faulty liver metabolism; others as the result of abnormal intestinal absorption. As stated by Beckh and Ellinger, it is specially found in secondary alcoholic pellagra, but Spies, Cooper and

Blankenhorn showed that the amount of coproporphyrin in the urine appears to be proportional to the nicotinic acid intake.

Symptoms.—The cardinal signs of pellagra constitute the well-known diagnostic triad : " diarrhœa, dermatitis and dementia." The course is generally long and irregular, one of repeated exacerbations and periods of quiescence. The initial symptoms are composed of mingled psychical and digestive disturbances which may recur for years without the appearance of skin eruptions. The patient is pale, has a peculiar lifeless staring look, with dilated pupils, and complains of headache, giddiness, and vague but often severe pains in the back and joints. The scleræ are bluish and leaden coloured. The eyelids move sluggishly ; the complexion is muddy. The character changes, becoming irritable, and at the same time stupid and morose.

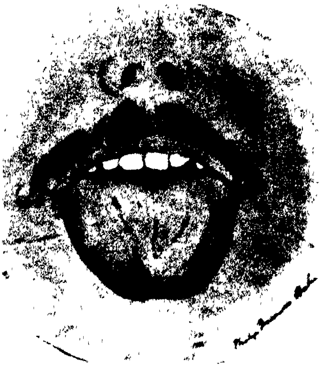
Observations on children in pellagrous families in the United States show that many have clinical signs of pellagra. They are below the normal weight and height for their years, they make slow progress at school, show lack of interest, inability to concentrate and have poor appetites. Their hearts are irritable and they may have tachycardia.

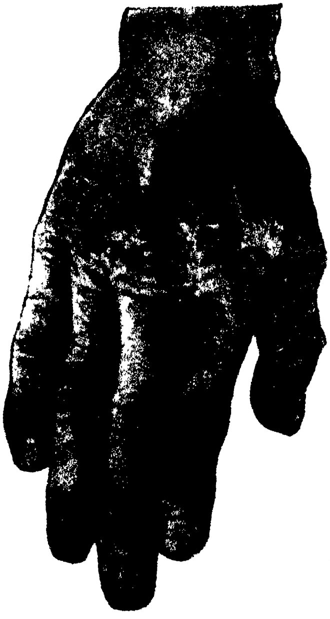
The earliest signs of a pellagrous tendency are difficult to define, as there are probably a great many people who suffer from chronic ill-health and are really in the pre-pellagrous state. This tendency may manifest itself by a peculiar stomatitis with erosions at the angles of the mouth (angular stomatitis) (Plate IX).[1] There may also be an atrophic condition of the lips (*perlèche*) to which the Editor drew attention in Ceylon in 1912 in prisoners who had been fed on dried fish (*see* p. 539). The pellagrous process may not proceed beyond this stage. On the other hand, it may be progressive and advance to a fully developed syndrome. Then the gums may be swollen and bleed easily, a condition which gave rise to the term " Alpine scurvy." There may be eructations of gas, nausea, and vomiting. The appetite is variable. The epigastric region and, sometimes, the lower abdomen are tense and painful. Constipation may be present, but in rare instances there is diarrhœa of pale fermenting stools resembling those of sprue.

The pellagrous rash.—Most observers regard the skin lesions of pellagra as early manifestations, but they are symptomatic of the underlying constitutional disturbances. At first an erythema, not unlike a severe sunburn, is observable on the parts of the body which are, as a rule, unclothed and exposed to the sun (Plates VIII, IX). The eruption is symmetrical and characteristic. It appears suddenly, first on the back of the hands and feet, then on the forearms, legs, chest, neck, face, and, it may be, on the scrotum or on female genitalia, anus and other regions subject to mechanical irritation. Patches of erythema are irregular in outline and intensity. Very characteristic is a symmetrical eruption behind the mastoid processes, a ring or collar round the neck (Casal's necklace), and a butterfly patch over the bridge of the nose resembling lupus erythematosus. The affected area is swollen and tense, and the seat of burning or itching sensations which become particularly acute on exposure to the sun. The congestion disappears completely, but temporarily, on pressure. Petechiæ are common on the affected parts ; blebs with clear, opaque, or blood-stained contents of

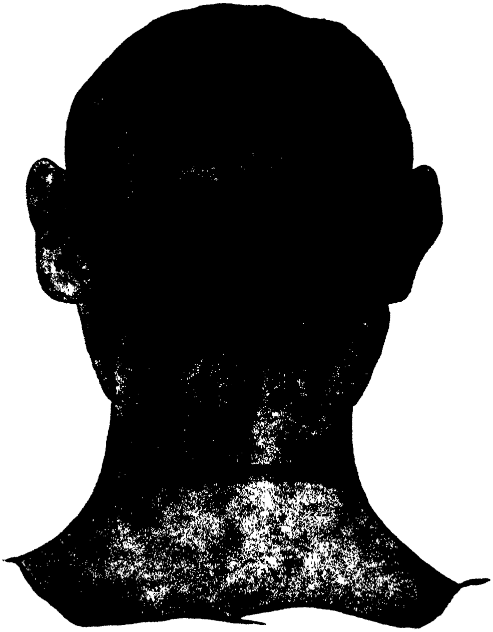
---

[1] Plummer-Vinson syndrome, p. 441.





2



3

Fig. 1. Characteristic inflamed tongue of acute pellagra with angular stomatitis.

Fig. 2. Early pellagrous rash, with cellular infiltration and pigmentation.

Fig. 3. Typical pellagrous rash over occiput and mastoid processes, with formation of "rosary" round neck.

PELLAGRA.

Plate IX

Fig. 3. (P. H. M.-B.)

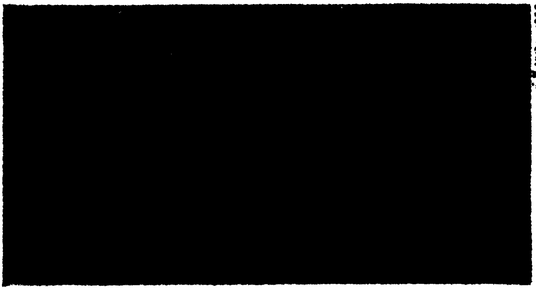


Fig. 2.

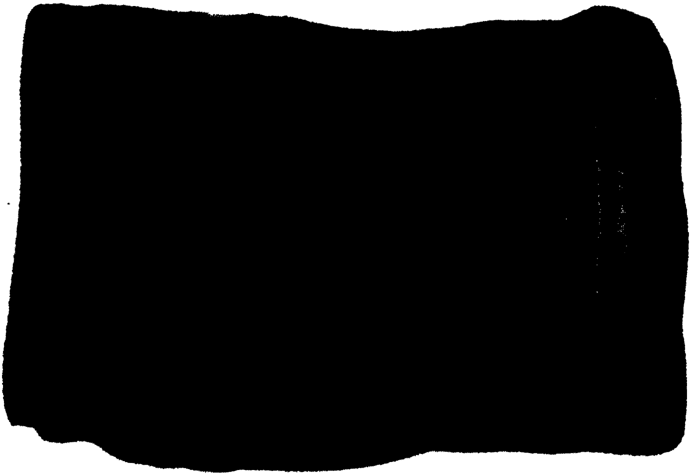


Fig. 1.—AMŒBIC DYSENTERY. Typical patches of infiltration and ulceration of ascending colon, showing "Dyak-hair" sloughs. Fig. 2.—BACILLARY DYSENTERY (Sonne infection): Acute Sonne dysentery in a child, showing bright pink hyperæmia of muscular coat. Fig. 3.—BACILLARY DYSENTERY (Shiga infection): Coagulation necrosis of lower portion of ileum, showing characteristic green coloration of the destroyed mucous membrane.

INTESTINAL LESIONS IN AMŒBIC AND BACILLARY DYSENTERY (*Half nat. size*).

feebly alkaline reaction may form. The eruption usually lasts about a fortnight, and is followed by hyperkeratosis and desquamation, which leaves the skin rough, thickened, and permanently stained a light sepia. This is especially marked on the back of the hands and on the elbows, thus constituting recognizable evidence of pellagra. Hyperkeratosis may occur on the soles of the feet and as diffuse thickening over the knuckles. In severe cases the skin over a large area of the body comes to resemble that of a roasted turkey. Ichthyotic changes sometimes supervene and may be more intense in winter than in summer. It is on account of this roughness of the skin that the disease was originally called " pellagra " (an Italian word derived from *pelle* (skin) and *agra* (rough)).

Stannus has suggested, as a result of the work of Lewis on the blood-vessels of the human skin and their responses, that the skin lesions in pellagra are due to the liberation of histamine and its action upon the blood-vessels, and that the mechanism underlying the affections of the mucous membranes is of a similar nature.

Exposure to light appears to be the precipitating factor. Ruffin and Smith showed that radiation may evoke not only skin lesions, but also associated oral, gastro-intestinal and neurological manifestations. Since injections of porphyrin can sensitize normal persons to sunlight, it has been suggested that there may be abnormal porphyrin metabolism in pellagra. The burning sensation in the soles of the feet and palms of the hands which is such a common symptom in pellagra may be ascribed to the same cause.

Naturally, the appearances of pellagra differ considerably in different races. What is an erythema in the European becomes a blackish or purplish patch on the skin of a negro. In olive-skinned races pellagrous patches assume a sepia colour.

Implication of the *nervous system* is indicated by tremor of the tongue, exaggerated deep reflexes, and mid-dorsal spinal tenderness. Coarse tremors of the extremities, especially of the head and the hands, are frequently noted and become more marked as the disease progresses. Muscular cramps may occur ; definite ankle clonus, spasticity and extensor-plantar response are often seen. The patient suffers from obstinate sleeplessness, occasionally from uncontrollable sleepiness. He experiences great weakness, especially in the lower extremities, and is subject to peculiar attacks of giddiness, with a tendency to fall forwards or backwards. Chvostek's sign—mechanical irritability of the facial nerves—is present in the majority of cases. A very characteristic symptom is pyrosis, or a burning sensation down the œsophagus (dysphagia). This frequently creates the idea in the patient's mind that his food does not agree with him, or even that attempts are being made to poison him. The pupils are dilated and there is usually photophobia. The arms may be spastic and movements are accompanied by a coarse tremor, which is increased on exertion.

After the disappearance of the eruption, atrophic patches of skin remain in the interdigital clefts, and these, together with muscular wasting, give the appearance of washerwomen's fingers. The hands, in fact, are aged out of proportion to the rest of the body. The nails become atrophied and brittle.

As a rule, there is no marked permanent elevation of temperature, but periods of slight fever occur at irregular intervals.

Progress.—Two or three months after onset the symptoms abate and, although the affected skin areas remain dark and rough, the disease appears to be arrested. Next spring, however, the whole series of phenomena recurs in a more severe form. The eruption assumes a darker colour. The depression of spirits deepens into melancholia, which may have maniacal interludes, with a peculiar tendency to suicide, especially by drowning. The general feeling of weakness increases ; the patient loses weight and is unable to work ; his gait becomes uncertain and somewhat of the spastic paraplegic type. The tongue is tremulous. The pains in the head and back become very acute, and there may be lightning pains, cramps, twitchings, tremors, and even epileptiform seizures of the cortical type. Diarrhœa may now be troublesome.

For several years the disease may thus recur in the spring with increasing severity. The patient becomes greatly emaciated, paralytic, and completely demented. Helpless, bedridden, suffering from incontinence of urine and uncontrollable diarrhœa, covered with bedsores, and neglected, he dies from exhaustion or from some intercurrent disease.

The duration of pellagra is exceedingly variable. It may last only two or three years ; it usually extends to ten, fifteen, or more.

Cases differ considerably. The obscure forms are probably much more common than the fully declared disease. They were formerly known—somewhat incongruously—as *pellagra sine pellagra.*

Ariboflavinosis.—The riboflavin deficiency syndrome is now regarded as typical of "*pellagra sine pellagra.*" The following signs are characteristic of it : angular stomatitis[1] and facial lesions consisting of filiform seborrhœic excrescences (dyssebacia), varying in length up to 1 mm., sparsely scattered over the face. The mouths of the sebaceous glands are plugged with inspissated sebum, giving the skin a roughened appearance, which on the shoulder, arms and legs is known as *phrynoderma* or toad's skin. The eyelids show dermatitis lesions, may be macerated and stuck together. Fissures and maceration at the angles of the mouth are seen, and a degenerative crust-like formation on the epithelium of the lips, most marked on the lower. The lips, particularly the lower, frequently show a marked increase in the ver- [illegible] scribed : the tongue is clean, the

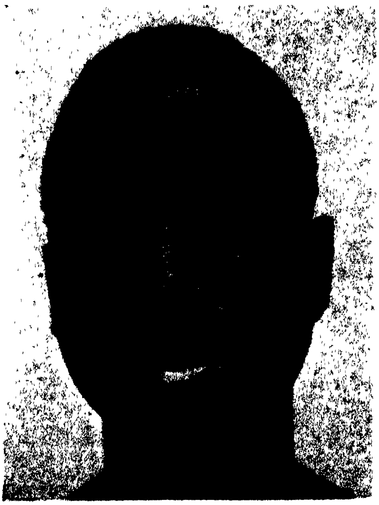


Fig. 63.—Avitaminosis B$_2$ in a West African negro. Characteristic facies of ariboflavinosis. (*Dr. D. Fitzgerald Moore.*)

---

[1] The term "cheilosis," applied by some writers to lesions at the angles of the mouth, should be reserved for lesions on the lips.

papillæ flattened or mushroom-shaped and the colour definitely purplish red or magenta, in contrast to the scarlet tongue of nicotinic acid deficiency. (Plate XVII.)

The ocular manifestations are burning, lachrymation, photophobia, blurred vision, inability to see in a dim light and visual fatigue. The earliest and most common sign is circumcorneal injection and, when viewed by a slit lamp, there is marked congestion and proliferation of the limbic plexus, with the production of great numbers of narrow capillary loops. The lesion progresses to vascularization of the cornea within a week, if treatment with riboflavin is not given. Eventually keratitis is produced, similar to that associated with acne rosacea, which is also amenable to riboflavin therapy. It is probable that ariboflavinosis is also responsible for retrobulbar neuritis, which may also be part of the pellagra syndrome (*see* p. 408).

Other less marked varieties (*Formes frustes*).—Corkhill and others have pointed out that there are quite a number of subclinical cases in which physical signs are less obvious, but symptoms appear only after undue fatigue.

In some the nervous symptoms predominate, in others the gastro-intestinal; in others again the cutaneous. Forms of hyperæsthesia may occur in different regions of the body, especially the feet (p. 427). Ocular symptoms, such as ptosis, diplopia, retrobulbar neuritis, amblyopia, mydriasis, are not uncommon. The Plummer-Vinson syndrome of glossitis and dysphagia, with angular stomatitis, koilonychia and anæmia, in aged women is possibly a pellagrous manifestation.

Infantile pellagra.—Pellagra in childhood is very apt to be overlooked, especially in native races. The children become irritable, their skin and hair tend to lose the normal colour and glossiness, and there may be attacks of diarrhœa with transient œdema of the hands, feet, and face. After ten days or so pigmented patches appear on the skin of the extensor surfaces about the ankes, knees, wrists and elbows, and these blackened patches appear first where there is any focus of irritation or pressure. Trowell described infantile pellagra in E. Africa as a syndrome of which the principal signs are œdema, dermatitis and diarrhœa; similar cases from W. Africa were described by Williams as "kwashiorkor." This is an acute form with nutritional œdema and decreased serum albumin. Infantile pellagra has also been reported in American negroes, from Mexico, Cuba, Costa Rica and S. China.

Pellagra typhus.—In this very acute type there are intense prostration, high temperature, muttering delirium, pronounced nervous tremor, generalized rigidity, and convulsions. In extensive outbreaks of pellagra, such as occurred among the Turks during the 1914–1918 war, cases of this description were comparatively common.

Terminal stages, pellagrous insanity:—Mental symptoms supervene in one-third to one-quarter of all cases.

It has been estimated that from 4 to 10 per cent. become permanently insane. In the United States of America pellagrins are becoming numerous in the lunatic asylums. The type of insanity is usually a most profound melancholia with a suicidal tendency; cases may resemble in their clinical features general paralysis of the insane. Epileptiform convulsions may occur.

The time of the appearance of mental symptoms is subject to the widest variation. They may be primary symptoms, or occur during convalescence. The mental aberrations may be characterized by profound dementia, hallucinations, and katatonia. As a rule, restlessness, vertigo and insomnia anticipate the characteristic melancholia. In general, the patients exhibit anxiety neurosis with depressive features. Pyschosensory disturbances are common, with intolerance of bright light, colours and noises. The patients are fidgety, quarrelsome and irritable. In spite of increased motor drive, they complain of weakness and fatigue.

Not only may pellagra lead to insanity, but those insane from other causes are very liable to pellagrous manifestations. Goldberger found that in certain asylums in the United States the number of lunatics developing pellagra each year was a constant proportion of the total. In England, pellagra has been noted in lunatic asylums since 1913. Watson, in a review of the pellagra cases in the Rainhill Asylum, Lancashire, found that at the time of onset they had been resident from six months to several years.

Secondary pellagra.—Pellagra due to voluntary restrictions of diet has been recognized by several observers during recent years. Mook and Weiss described the typical clinical picture of pellagra in a young woman on a slimming diet; Mumford, Carley and others found it in mature women who, for some faddist cult, had been subsisting on an unbalanced dietary; Guthrie, Green, Walker and Wheeler reported similar phenomena in patients on a ketogenic régime.

Pellagra in all its varied manifestations may be associated with some organic lesion in the gastro-intestinal tract, such as œsophageal stricture, carcinoma of the stomach, pyloric ulcer, pyloric stenosis, carcinoma of the ileum, stricture of the rectum, rectal polyposis, suppurating hydatid cyst, chronic amœbic dysentery, cœliac disease, or idiopathic steatorrhœa; the Editor recorded one case in association with sprue. When the avitaminosis follows surgical operations, such as partial colectomy, on the gastro-intestinal tract or elsewhere, it is known as *surgical pellagra*. *Alcoholic pellagra* is applied by American observers to the disease in chronic alcoholics, especially those who drink methyl alcohol. It has been suggested by Stannus, by way of explanation, that gastritis is the one common factor which supports the hypothesis that, primarily, in pellagra the fault may lie in the intrinsic factor of the gastric juice.

Diagnosis.—Doubtful cases are occasionally encountered, but localized erythema associated with nervous, particularly mental, symptoms, great debility, and seasonal recurrence, in a person in or coming from a pellagrous district, can hardly be confounded with any other disease. The rash may be mistaken for acrodynia, erythema multiforme, dermatitis venenata, eczema solare, trade dermatitis, lupus erythematosus, syphilis, or poison-ivy dermatitis. "Crazy pavement" skin lesions, which are common on the legs of ill-conditioned natives, are not necessarily pellagrous. The gastro-intestinal disturbance and glossitis have to be distinguished from sprue; while the nervous manifestations have to be differentiated from hysteria, cerebral syphilis, general paralysis of the insane, ergotism, and lathyrism. In old people with arterio-sclerotic changes and accompanying mental symptoms, there may be lesions of hands and feet which may be a source of confusion. " Pink disease " in children may also be mistaken for pellagra, as the distribution of the skin lesions is very similar.

Treatment.—After the end of the 1914–1918 war and the formulation of the *biological protein theory*, many workers, notably Goldberger and Wheeler, noted that improvement in the pellagrous lesions, and even in the nervous involvement, followed a liberal dietary rich in proteins and in vitamins. Then ensued a period in which liver and yeast extracts, notably marmite, were given an extensive trial, but it was generally conceded that, though the therapeutic secret was locked up in the vitamin-B complex, vitamin B_1 was not the main factor.

In 1937 Elvehjem, Madden, Strong, and Wooley reported the cure of black-tongue in dogs by the administration of nicotinamide prepared from yeast. Shortly afterwards Spies, Cooper, and Blankenhorn recorded the successful treatment of human pellagra cases. These patients were in hospital and received a controlled basal diet, upon which alone symptoms had shown no improvement. Relatively large doses of *nicotinic acid* were given—40–80 mgm. by injection, or 200–1,500 mgm. by the mouth within a period of twenty-four hours. Almost simultaneously, Fouts, Helmer, Lepkovsky, and Jukes reported the cure of four cases of " alcoholic pellagra " treated on the same lines, there being improvement in the mental condition, stomatitis, and the intestinal disorders, as well as cure of the dermatitis. Spies, Bean, and Stone (1938) then published a series of 73 cases of endemic pellagra and 99 of " subclinical pellagra ", and stated that they had not observed a single acute case that had not responded promptly to nicotinic-acid therapy. Also, in a special study by Spies, Aring, Gelperin, and Stone of 60 cases showing acute mental disorder, improvement was observed within periods of ten hours to six days after nicotinic acid medication, the daily dosage being 500–1,000 mgm. by mouth, or 100 mgm. intravenously. Further confirmation soon came from Matthews, who studied 13 cases of classical endemic pellagra maintained on a pellagra dietary. These favourable results in American pellagra have received a considerable degree of confirmation in the hands of Alport, Ghaligoungui, and Hanna in Egypt, and also of Ellinger, Hassan, and Taha (1937). They treated 15 cases with nicotinamide (Merck), the dose being 1 grm. daily by the mouth or 0·5 grm. by subcutaneous injection. On the whole, they found that acute inflammation of the tongue and ulceration of the mouth subsided in five to seven days, and the sense of taste returned in the same time; in one case colic supervened almost immediately, suggesting intolerance. Thus nicotinamide effected great improvement in the acute mucous membrane lesions, as well as in the skin condition; on the other hand, chronic skin lesions, friction areas and chronic changes in the tongue were only slightly affected. The appetite, mental condition and general physical health were all improved. Grant and Spies recorded that ptyalism, Vincent's infection and coproporphyrinuria disappeared, and Hawksley found great change in the follicular hyperkeratosis on and around the naso-labial folds.

Since the discovery of ariboflavinosis as part of the pellagra syndrome most authorities reinforce treatment with riboflavin tablets in doses of 1–3 mgm. daily. During the recent outbreak of pellagra in Hong Kong Wilkinson found the effects of intravenous nicotinamide injections almost dramatic. Patients who were disorientated, rambling in speech and unable to co-operate or swallow, became hungry and rational within 72 hours. (In acute pellagra the blood nicotinic acid was found to be 0·31 mgm. per cent. and to rise on treatment to 0·55 mgm. per cent.). In cases with rapidly increasing reduction of visual acuity, associated with concentric constriction of fields of vision, response to nicotinic acid and riboflavin daily changed the vision from 6/60 to 6/9 or 6/6 within a week.

The evidence that nicotinic acid is a specific cure for pellagra and for the somewhat similar nutritional diseases produced by maize diets in dogs and pigs (Chick, Macrae, and Martin) thus appears to be conclusive, and it is now reasonable to ascribe the curative value of liver extracts and yeast, formerly observed in pellagra, to their nicotinic acid content. Ruffin and Smith (1937) found that, whereas crude liver products were effective in relatively small doses in canine blacktongue and in pellagra, larger amounts of more purified extracts were ineffective. These observations, which suggest that a combination of two substances is needed to correct deficiencies in diets which induce blacktongue and pellagra, are difficult to reconcile with the curative effect of such simple substances as nicotinic acid and nicotinamide.

The reaction to nicotinic acid in normal individuals is tingling and increased warmth over the malar regions and neck. Sometimes nausea, vomiting, abdominal cramps and urticaria may ensue. Nicotinic acid and nicotinamide are now dispensed in a convenient form in tablets of 30 to 50 mgm. each. In mild cases 50 mgm. is given three times daily (150 mgm.) for ten to fourteen days, and double that quantity (300 mgm.) in more severe cases. The effect of this treatment upon the pellagrous rash is impressive. Overdosage causes some tingling and numbness of the tongue, and also in the lower jaw along the course of the inferior dental nerve. This treatment should, of course, be backed up by a liberal protein dietary. Riboflavin in maximal doses (3 mgm.) should be added in cases exhibiting signs of ariboflavinosis. The most striking and most easily observable effect of this mode of treatment is seen in the amelioration of the tongue and mouth symptoms. It has a profound effect upon the psychology of the patient as well as on the processes of digestion and assimilation.

The treatment of mental symptoms.—Spies, Aring, Gelperin and Bean submitted 60 cases with mental manifestations to treatment with nicotinic acid, in maximum doses, and *coramine* (the diethylamide of nicotinic acid). These cases showed loss of memory, delirium, mania, or depression ; some had a paranoid reaction. Recovery took place in all within six days. Korsakoff's psychosis and manic depressions were not influenced in the same way. Coramine is injected in doses of 2–5 c.c. daily by the mouth to a total of 20–50 c.c.

Treatment with allied preparations.—Certain of the pyridine carboxylic acids exhibit anti-pellagrous properties. Bills, McDonald and Spies found that pyrazine 2–3 dicarboxylic and pyrazine monocarboxylic acid act like nicotinic acid, curing glossitis and dermatitis. Vilter and Spies claimed that quinolinic acid (2-3–dicarboxylic acid of pyridine) has a therapeutic action on the tongue and mouth symptoms.

Prophylaxis.—In view of the volume and importance of recent researches in this field, it is evident that the prophylaxis of pellagra is bound up in public-health measures and especially in ensuring a well-balanced protein dietary. Whether pellagra can be prevented by the prophylactic administration of nicotinic acid and riboflavin remains to be seen.

CHAPTER XXVI

SCURVY IN THE TROPICS

EPIDEMICS of scurvy are apt to occur among gangs of coolies and labourers who are fed on an unsuitable dietary, especially in natives recruited for labour purposes and fed upon dried cereals and preserved foods, who previously had been in the habit, in their own villages, of subsisting on large quantities of fresh vegetables and fruit such as bananas.

Ætiology.—Scurvy is a food-deficiency disease. It is produced, not by general starvation, but by the absence of an accessory food factor, or vitamin, which can now be prepared synthetically and is known as ascorbic acid. This body (p. 407) is present in all fresh vegetables, including swedes, turnips, and onions, and in fresh fruit, especially the orange and lemon. It is very sensitive to prolonged heat and drying, and therefore is absent from tinned fruits and vegetables, and from dried legumes such as peas and beans, but re-appears directly the latter are induced to germinate. Yeast, fresh meat, and milk contain only small quantities of the antiscorbutic vitamin, and, curious to relate, according to Chick and Hume, preserved *lime* juice little or none at all, while preserved lemon-juice is rich in this substance.

History.—Scurvy was found to be prevented by diet by Kramer (1720); Lind's " Treatise on Scurvy " was published in 1857 ; infantile scurvy was recognized as a dietetic disease by Barlow (1883). Laboratory experiments by Holst, Frölich, Zilva, Mellanby and others (1907-1929) led to the discovery of vitamin C. The identity of vitamin C and hexuronic acid (ascorbic acid), suggested by Tillmans and Hirsch (1928) was proved by Szent-Györgyi (1928). The constitution was established by Haworth, Hirst and Reichstein (1933), and synthesis effected by Haworth and Reichstein in 1934.

Symptoms.—The onset of scurvy is insidious, with loss of weight, progressive weakness and pallor, and a feeling of stiffness in the leg muscles. The gums soon become affected with a swelling and sponginess of the alveolar margin. As the disease progresses, fungating masses project beyond the teeth, which loosen and fall out. The tongue swells, the salivary and lymphatic glands enlarge, and the breath becomes very foul. The skin becomes dry and rough, and very soon subcutaneous petechiæ form on the limbs and trunk, commencing *around the hair follicles*, especially on the thigh (Fig. 64). Hæmorrhages occur into the muscles of the thigh and into the knee-joint. Very painful

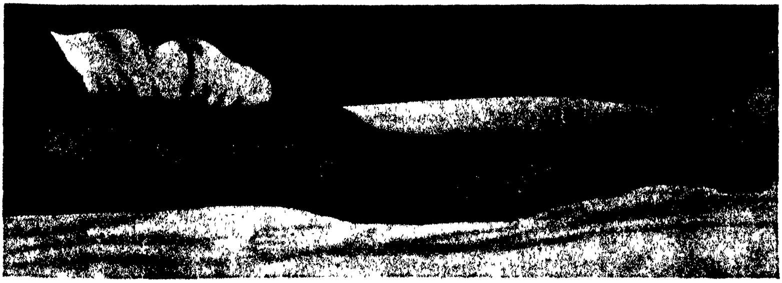


Fig. 64. Scurvy rash in sprue, showing distribution of petechiæ round hair follicles.

effusions under the periosteum form irregular nodes, which may break down and ulcerate. Œdema of the ankles is common, and hæmoptysis or hæmatemesis may occur. Any injury is apt to cause a hæmorrhage.

Together with these objective symptoms the patient experiences cardiac distress, with irregularity of the pulse and hæmic bruits at the apex. The urine is generally loaded with albumin. On the other hand, the digestive system is not disturbed, constipation being more common than diarrhœa. The psychical disturbances are pronounced. Headache is noted early, and delirium supervenes in the later stages. In the most advanced cases the jaw-bones generally become necrotic.

In the young the formation of a "scurvy rosary" at the junction of the costal cartilages, and separation of the epiphyses of the long bones, may occur in a variety known as infantile scurvy, or Barlow's disease.

Scurvy was formerly noted as endemic in the mine-workers on the Rand. Darling and others observed that a certain proportion of these cases was distinct in a clinical sense from those seen elsewhere. In this variety, known as *Rand scurvy*, the spongy gums and loose teeth that occur in the classical type of the disease were absent, while the heart underwent primary hypertrophy, with subsequent dilatation, suggestive of beriberi, though the neuritic symptoms of beriberi were absent, and the knee-jerks exaggerated. Rand scurvy occurred especially among gangs of native labourers when fed upon an unsuitable dietary, particularly natives from the Congo and tropical Africa, who were in the habit of consuming large quantities of fresh vegetables and fruits, and who, when in the mines, were fed on dried cereals and preserved foods. The number of these cases was very large indeed. Donaldson reported that in 1920 more than 200 cases of scurvy were treated in one hospital, of which one-third occurred within three months of entering the mines. It was found that scurvy in these natives predisposed to all kinds of bacterial infections, and especially to pneumonia. Where the diet was deficient but not entirely lacking in vitamin C, actual symptoms of scurvy did not manifest themselves, but such individuals were very liable to bacterial infections owing to degenerative changes in the bone-marrow.

Diagnosis.—To diagnose scurvy under modern conditions is no difficult matter; but care must be taken to distinguish mild cases from pyorrhœa alveolaris. A method of diagnosis in the early stages, especially in children, was devised by Hess. The arm-band of a sphygmomanometer is placed upon the arm and inflated until the pressure reaches 90 mm., and the venous circulation is shut off. This pressure should be maintained for three minutes and then released. As soon as the cyanosis fades, an examination should be made for the petechial spots which may confirm the diagnosis of scurvy. This test depends on increased fragility of the capillary endothelium. Rotter introduced an *intradermal test* with dichlorphenol-indophenol. (For the technique of this test, as well as of the demonstration of vitamin C in the urine, *see* p. 410.)

Differential diagnosis has to be made from blood diseases such as leukæmia, and essential thrombocytopenia (onyalai, *see* p. 673).

Treatment.—This is chiefly dietetic. The disease, if recognized early, readily yields to a diet composed of fresh fruit and vegetables; when these are unprocurable, fresh meat can be substituted, but is by no means so satisfactory.

Raw onions are very valuable antiscorbutics, and raw potatoes and swedes have a definite curative value. Canned vegetables, except canned tomatoes, are useless.

For natives, the most valuable antiscorbutic foods are orange, lemon, and pawpaw juice, sweet potatoes, and green mealies. Incompletely fermented beer, such as the Kaffir beer, made from germinating grain, is said to be of considerable value, but this is doubtful.

Vaughan, Hunter and others reported brilliant successes in the treatment of scurvy with synthetic ascorbic acid. Many cases were reported by Schultzer, Parsons, Harris, Ray, and Szent-Györgyi; 40–100 mgm. of ascorbic acid are given intravenously to an adult for ten days with success; to infants 30–60 mgm. daily by the mouth for about fourteen days.

Germinating peas are useful when fresh vegetables are unobtainable. The following method of using peas and other pulses is recommended by Chick and Hume:

SUGGESTED METHODS OF PREPARING PEAS, LENTILS, OR OTHER PULSES FOR THE PREVENTION OF SCURVY, IN THE ABSENCE OF FRESH VEGETABLES

1. The dry seeds must be whole, retaining the original seed-coat, and not milled or decorticated.

2. They must be soaked in water for several hours; the time necessary depends on the temperature—24 hours at 50° to 60° F., and 12 hours or less at 90° F.

3. The water must then be drained away, and the peas allowed to remain moist with access of air. They will then germinate and the small rootlet grow out. This germination will take 48 hours at 50° to 60° F., and 12 to 24 hours at 80° F.

Soaking.—The peas or other pulses, placed in a *clean* sack, should be steeped in a trough, barrel, or other suitable vessel, full of clean water, and should be occasionally stirred. The sack and trough should be large enough to allow for the swelling of the peas to about three times their original size. In a hot climate 6 to 12 hours should suffice for this soaking.

Germination.—The peas should be lifted out of the water and spread out to a *depth not exceeding 2 to 3 inches* in a trough or other vessel with sides and bottom porous or well perforated with holes; this is to allow *complete* access of air. *The seeds must be kept in a moist atmosphere*, by covering with damp cloth or sacking, which is sprinkled (by hand or automatically) as often as is required to keep the peas thoroughly moist underneath. *All the vessels should be clean.*

4. *It is important that the germinated pulses should be cooked and eaten as soon as possible after germination, and should not be allowed to become dry again*; in that case the antiscorbutic properties acquired during the process of germination will again be destroyed. The pulses should not be cooked longer than necessary.

Prophylaxis.—The prevention of scurvy consists in providing a diet adequate in vitamin C. It should be the duty of health authorities and medical officers of industrial undertakings to insist that native labourers are adequately fed. The old and evil idea that African natives can subsist on maize meal, salt and dried beans should be most vigorously suppressed. It has been pointed out that one factor in the production of scurvy in native African races is the prolonged overcooking[1] and steaming of food, especially of vegetables. It is, therefore, important that in gangs of unmarried natives efficient cooks should be appointed. As a general rule, the food cooked by native women is much more hygienic and palatable than that prepared by men.

Wherever possible, in mines or tropical camps, native gardens should be established. Men threatened with scurvy should be given light work only.

---

[1] When cabbage is cooked for one hour at temperatures ranging from 80–100° C. the leaves lose 90 per cent. of their antiscorbutic value.

Ætiology. *Discovery of the comma bacillus, or vibrio.*—The cholera vibrio was first discovered by Koch in Egypt in 1883; this discovery he confirmed in Calcutta in 1884 by finding it in every case of the disease examined. His observations have since been abundantly confirmed.

Description of the cholera vibrio.—The comma bacillus (Fig. 65) is a very minute organism, 1·5 to 2 μ in length by 0·5 to 0·6 μ in diameter—about half the length and twice the thickness of the tubercle bacillus. It is generally slightly curved like a comma; hence its name. After appropriate staining, flagella can be distinguished at each end or at one end only—sometimes one, sometimes (though less frequently) two. These flagella, though of considerable length—from one to five times that of the body of the bacillus—are difficult to see in ordinary preparations owing to their extreme tenuity. They are not always present during the entire life of the parasite. They impart very active spirillum-like movements. The individual bacilli, when stained, show darker parts at the ends or at the centre. Sometimes in cultures two or more bacilli are united, in which case an S-shaped body is the result; or several bacilli may be thus united, producing a spirillar appearance.

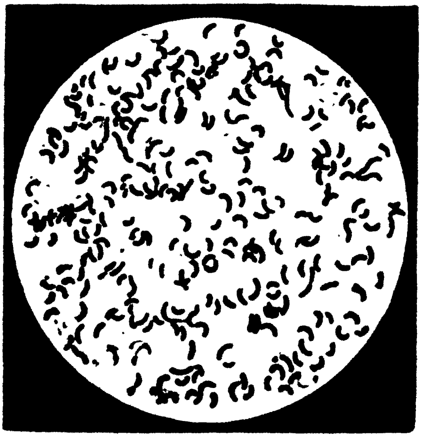


Fig. 65.—Cholera vibrio. Agar culture: 24 hours' growth. × 1,000. (*Muir and Ritchie.*)

The comma bacillus is easily stained by watery solutions of fuchsin, or by Löffler's method, dried cover-glass films being used. It is decolorized by Gram.

The bacillus grows best in alkaline media at a temperature of from 30° to 40° C. Growth is arrested below 15° or above 42° C.; a temperature over 50° C. kills the vibrio. Meat broth, blood-serum, nutrient gelatin, and potato are all suitable culture media. It multiplies rapidly without curdling in milk; it dies rapidly in distilled water; it survives longer if salt be added to the water—for instance, 285 days in sea-water.

In gelatin plates it grows readily as minute white colonies, irregular in shape, and granular, with surrounding liquefaction, into which the colonies of vibrios sink as into funnel-shaped depressions. In gelatin stab-cultures the growth at first is most active near the surface; later, as growth proceeds along the needle track, a finger-shaped liquefaction results, which in time extends to the sides of the tube. In older cultures involution forms are common; they may die out after five or six weeks.

Agar is not liquefied, and in it cultures retain their vitality longer. On potato, at 20° to 30° C., the culture appears as a thin, brownish, porcelain-like film. In broth some of the bacilli form a scum on the surface; others, falling in masses to the bottom, leave the body of the liquid clear. As a rule, the cholera vibrio does not produce hæmolysis, if blood be added to the medium such as agar, after twenty-four hours' incubation. The test is best performed in a fluid medium by adding varying amounts, from 1 c.c. downwards, of a three days' culture in alkaline broth to 1 c.c. of a 5 per cent. suspension of goat's corpuscles, and then thoroughly mixing. After incubation for two hours the tubes are placed in the ice-chest overnight and read the next day. With the solutions of sugars (1 per cent.) usually employed, the vibrio produces acid, without gas-formation, in glucose, mannite, saccharose, and maltose. Fermentation of lactose, with acid production, occurs two or three days later. The cholera-red reaction is obtained by the addition of pure sulphuric acid to a culture in 1 per cent. peptone solution.

The true cholera vibrio belongs to Heiberg's Type I, and ferments mannose and saccharose, but not arabinose. It gives positive cholera red and negative Voges-Proskauer reactions; but does not produce early hæmolysis of erythrocytes. These characters alone, however, are not enough for more than presumptive identification, since some non-pathogenic vibrios have most of them. The true cholera vibrio is agglutinated by serum prepared against the O variants of Ogawa and Inaba strains, and this is the principal means of differentiation (Gardner and Venkatraman).

Until recently a considerable amount of hesitation was felt by many authorities in accepting the cholera vibrio as the true germ-cause of cholera.

Certain organisms, known as the paracholera, or inagglutinable vibrios (Finkler-Prior and El-Tor), resemble the cholera vibrio minutely. Organisms found in fowl cholera, in decomposed cheese, and in river water also resemble it very closely but, as they behave somewhat differently in the serological sense, they must be considered biologically distinct. Cultures of cholera vibrios have been swallowed many times by way of experiment, and, although in some instances diarrhœa has resulted, in only one case has true cholera been produced. Probably for the production of cholera several conditions are necessary, of which the comma bacillus is only one. The difficulty of producing true cholera in lower animals by the administration of cholera cultures has exercised the minds of many, especially in the days following Koch's discovery, but more recently cholera-like symptoms have been produced in ground-squirrels by administering cultures of the organisms in alkaline media.

The exact significance of the non-agglutinating vibrios still remains a matter of debate. Doorenbos brought forward evidence that the El-Tor vibrio and other vibrios which behave somewhat differently are, in fact, the true cholera vibrio contaminated with bacteriophage. Formerly the association of epidemic cholera with a hæmolytic El-Tor vibrio was not considered possible, but de Moor and others in 1938 found that the epidemic in Celebes was caused by a typical El-Tor vibrio as shown by its cultural and serological characters. This vibrio belongs to Gardner and Venkatraman's subgroup O, Heiberg's type I, and is hæmolytic to goat cells. The epidemic caused by it came to an end in six months and did not occur again. This vibrio gave positive Voges-Proskauer and cholera red reactions and the agglutinability was not affected by heat as in the true cholera vibrio. Taylor regarded this form as practically non-existent in India in man, but as representative of certain water vibrios in Bengal. The general conclusion is that the two vibrios, though identical in antigenic structure, do represent different species and that the El-Tor vibrio occupies an intermediate position

Section III.—ABDOMINAL DISEASES

CHAPTER XXVII

CHOLERA

Synonym. Cholera Asiatica.

Definition.—Cholera (Χοληροια = flow of bile) is an acute, infectious, epidemic disease, characterized by profuse purging and vomiting of a colourless watery material, by muscular cramps, suppression of urine, algidity and collapse, the presence of the cholera vibrio in the intestines, and by a high mortality.

History and geographical distribution.—It is probable that from remotest antiquity cholera has been endemic in Lower Bengal and in Central China, and has from time to time spread as an epidemic over India. In 1817 it began to extend all over Asia, eastwards as far as Peking and Japan, southwards to Mauritius, and westwards to Syria and the eastern shores of the Caspian. Stopping short at Astrakhan in 1825, it did not on that occasion invade Europe. Since 1830, when cholera first visited Europe, there have been at least five epidemics—1848–51, 1851–55, 1865–74, 1884–86, and 1892–95. Minor epidemics have occurred in Europe since, but have been restricted. During the Balkan War of 1913, and in the course of the 1914–18 war, especially in the Balkans and in Iraq, there were many outbreaks of cholera, but the disease did not extend as an epidemic beyond the actual seat of war.

The 1870–73 epidemic practically spared Great Britain, but it crossed the Atlantic and, entering by way of Jamaica and New Orleans, raged for a time in the United States.

From a study of the march of these epidemics it is to be concluded that cholera reaches Europe by three distinct routes—(1) *via* Afghanistan, Persia, the Caspian Sea, and the Volga valley; (2) *via* the Persian Gulf, Syria, Asia Minor, Turkey in Europe, and the Mediterranean; (3) *via* the Red Sea, Egypt, and the Mediterranean.

Epidemiology and endemiology.—Cholera follows the great routes of human intercourse, and is conveyed chiefly by man—probably in its principal extensions by man alone—from place to place. In India, during religious gatherings, hundreds of thousands of human beings are collected together under highly insanitary conditions, as at the Hurdwar and Mecca pilgrimages. Cholera breaks out among the devotees, who, when they separate, carry the disease along with them as they proceed towards their homes, infecting the people of places they pass through. The Hedjaz has, for the last 100 years, been the point of relay of cholera in its progress from the Far East towards the West. During that period there have been more than 27 outbreaks. In India cholera appears to spread from its home in Lower Bengal over the northern and western, central, and southern provinces in a series of waves of two to four years' duration. Cholera never travels faster than a man can travel; but in modern times, owing to the increased speed of locomotion and the increased amount of travel, epidemics advance more rapidly and pursue a more erratic course than they did eighty years ago. On the other hand, isolated countries, such as the Andaman

Islands, Australia, New Zealand, the Pacific islands, the Cape Province, and the West Coast of Africa, have so far escaped. An epidemic of considerable virulence occurred in Celebes (Dutch East Indies) in 1938 and exhibited several peculiar features.

Truly endemic cholera centres are found in Lower Bengal and in the Yangtse Valley, China. According to Taylor, the recognition of an endemic area is :—

(*a*) one in which the total number of months with absence of cholera deaths does not exceed 30 in 32 years ;

(*b*) one in which a break of five or more months in cholera incidence does not take place.

There are two types of outbreak of cholera, according to whether the general water-supply is contaminated or contamination is localized to certain wells, cisterns, etc. In the former instance the outbreak is explosive and cases occur simultaneously in all parts of the city and disappear again with almost equal suddenness. In the Hamburg epidemic of 1892, during a period of only two months, cholera attacked 17,000 persons, causing 8,605 deaths in a population of 600,000. The water-supply of Hamburg was taken directly from the river, while the adjoining city, Altona (population 140,000) filtered its water from the river by a slow sand process. Although Altona lies further down the river and is contaminated with the sewage of Hamburg, yet the deaths in Altona were only 2·1 per mille as against 13·4 per mille for Hamburg. To illustrate the second type of transmission, there is the well-known incident of the Broad Street pump in 1854. This was the first definite proof of the association of cholera with water. It was noted that cholera was ten times more prevalent in Golden Square than in other parts of London, and increased in the neighbourhood of the Broad Street well. The employees of a factory where the well water was used had a large number of cases, while an adjoining brewery which had a well of its own did not furnish a single case.

Rogers believed that the condition necessary for the spread of cholera in India is an absolute humidity of over 0·400, and that by watching the climatic conditions which influence the seasonal and annual incidence of cholera, increased or epidemic prevalence should usually be foreseen in time for steps to be taken to lessen its spread.

The forecasting of cholera epidemics has therefore become an actual possibility. Based upon statistics which have been subjected to modern scientific analysis, an outbreak can be predicted two to three months ahead. All the co-efficients of correlation between the measure of cholera incidence and other variables to the highest order have been taken into consideration. The association of high relative humidity with high temperature, accompanied by intermittent rains, forms the most favourable atmosphere for the development of the disease, and the presence of endemic centres, from which epidemics may at any time spring, must also be accepted. Indian observers have recently found, on analysis according to the periodogram method, that in South India cholera occurs in a periodicity of six years.

D'Herelle made the interesting suggestion that the rise and fall of epidemics of cholera may be due to the amount of bacteriophage produced. Patients in whose stools no bacteriophage appears die of cholera. Those cases in whom bacteriophage is strong from the outset, rapidly recover.

Ætiology. *Discovery of the comma bacillus, or vibrio.*—The cholera vibrio was first discovered by Koch in Egypt in 1883; this discovery he confirmed in Calcutta in 1884 by finding it in every case of the disease examined. His observations have since been abundantly confirmed.

Description of the cholera vibrio.—The comma bacillus (Fig. 65) is a very minute organism, 1·5 to 2 μ in length by 0·5 to 0·6 μ in diameter—about half the length and twice the thickness of the tubercle bacillus. It is generally slightly curved like a comma; hence its name. After appropriate staining, flagella can be distinguished at each end or at one end only—sometimes one, sometimes (though less frequently) two. These flagella, though of considerable length—from one to five times that of the body of the bacillus—are difficult to see in ordinary preparations owing to their extreme tenuity. They are not always present during the entire life of the parasite. They impart very active spirillum-like movements. The individual bacilli, when stained, show darker parts at the ends or at the centre. Sometimes in cultures two or more bacilli are united, in which case an S-shaped body is the result; or several bacilli may be thus united, producing a spirillar appearance.

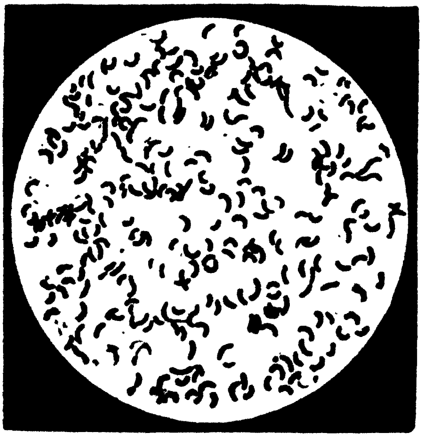


Fig. 65.—Cholera vibrio. Agar culture: 24 hours' growth. × 1,000. (*Muir and Ritchie.*)

The comma bacillus is easily stained by watery solutions of fuchsin, or by Löffler's method, dried cover-glass films being used. It is decolorized by Gram.

The bacillus grows best in alkaline media at a temperature of from 30° to 40° C. Growth is arrested below 16° or above 42° C.; a temperature over 50° C. kills the vibrio. Meat broth, blood-serum, nutrient gelatin, and potato are all suitable culture media. It multiplies rapidly without curdling in milk; it dies rapidly in distilled water; it survives longer if salt be added to the water—for instance, 285 days in sea-water.

In gelatin plates it grows readily as minute white colonies, irregular in shape, and granular, with surrounding liquefaction, into which the colonies of vibrios sink as into funnel-shaped depressions. In gelatin stab-cultures the growth at first is most active near the surface; later, as growth proceeds along the needle track, a finger-shaped liquefaction results, which in time extends to the sides of the tube. In older cultures involution forms are common; they may die out after five or six weeks.

Agar is not liquefied, and in it cultures retain their vitality longer. On potato, at 20° to 30° C., the culture appears as a thin, brownish, porcelain-like film. In broth some of the bacilli form a scum on the surface; others, falling in masses to the bottom, leave the body of the liquid clear. As a rule, the cholera vibrio does not produce hæmolysis, if blood be added to the medium such as agar, after twenty-four hours' incubation. The test is best performed in a fluid medium by adding varying amounts, from 1 c.c. downwards, of a three days' culture in alkaline broth to 1 c.c. of a 5 per cent. suspension of goat's corpuscles, and then thoroughly mixing. After incubation for two hours the tubes are placed in the ice-chest overnight and read the next day. With the solutions of sugars (1 per cent.) usually employed, the vibrio produces acid, without gas-formation, in glucose, mannite, saccharose, and maltose. Fermentation of lactose, with acid production, occurs two or three days later. The cholera-red reaction is obtained by the addition of pure sulphuric acid to a culture in 1 per cent. peptone solution.

The true cholera vibrio belongs to Heiberg's Type I, and ferments mannose and saccharose, but not arabinose. It gives positive cholera red and negative Voges-Proskauer reactions; but does not produce early hæmolysis of erythrocytes. These characters alone, however, are not enough for more than presumptive identification, since some non-pathogenic vibrios have most of them. The true cholera vibrio is agglutinated by serum prepared against the O variants of Ogawa and Inaba strains, and this is the principal means of differentiation (Gardner and Venkatraman).

Until recently a considerable amount of hesitation was felt by many authorities in accepting the cholera vibrio as the true germ-cause of cholera.

Certain organisms, known as the paracholera, or inagglutinable vibrios (Finkler-Prior and El-Tor), resemble the cholera vibrio minutely. Organisms found in fowl cholera, in decomposed cheese, and in river water also resemble it very closely but, as they behave somewhat differently in the serological sense, they must be considered biologically distinct. Cultures of cholera vibrios have been swallowed many times by way of experiment, and, although in some instances diarrhœa has resulted, in only one case has true cholera been produced. Probably for the production of cholera several conditions are necessary, of which the comma bacillus is only one. The difficulty of producing true cholera in lower animals by the administration of cholera cultures has exercised the minds of many, especially in the days following Koch's discovery, but more recently cholera-like symptoms have been produced in ground-squirrels by administering cultures of the organisms in alkaline media.

The exact significance of the non-agglutinating vibrios still remains a matter of debate. Doorenbos brought forward evidence that the El-Tor vibrio and other vibrios which behave somewhat differently are, in fact, the true cholera vibrio contaminated with bacteriophage. Formerly the association of epidemic cholera with a hæmolytic El-Tor vibrio was not considered possible, but de Moor and others in 1938 found that the epidemic in Celebes was caused by a typical El-Tor vibrio as shown by its cultural and serological characters. This vibrio belongs to Gardner and Venkatraman's subgroup O, Heiberg's type I, and is hæmolytic to goat cells. The epidemic caused by it came to an end in six months and did not occur again. This vibrio gave positive Voges-Proskauer and cholera red reactions and the agglutinability was not affected by heat as in the true cholera vibrio. Taylor regarded this form as practically non-existent in India in man, but as representative of certain water vibrios in Bengal. The general conclusion is that the two vibrios, though identical in antigenic structure, do represent different species and that the El-Tor vibrio occupies an intermediate position

between the cholera and non-agglutinable vibrios. The virulence of the cholera vibrio can be exalted by passage through guinea-pigs and successive culturing of the peritoneal exudate of intraperitoneally injected animals alternating with culture media growth inoculations. Such a fixed virus, the virulence of which cannot be exalted, formed the material used by Haffkine for cholera vaccine.

Gardner and Venkatraman (1935) made a thorough examination of the whole cholera-group question. They found that heat-stable antigens are divisible into: (*a*) a considerable number of specific antigens which are best demonstrated by O group sera and H-O suspensions, which serve as a basis of classification into O subgroups, and (*b*) a non-specific component which is demonstrable with O sera and O suspensions.

Taylor conducted an investigation on the serology of vibrios in which a standard O antigen was used. This is prepared in a dry form and testing sera were prepared from this dried antigen. Two main subtypes of *V. choleræ* were used which contained the common O and in addition its own specific antigen. The result indicated that vibrios isolated from true cholera cases, but which do not conform to the serological O group I, are mere accompaniments of the true cholera vibrio and are intestinal inhabitants as much of the non-cholera as of the cholera-stricken population.

Toxins.—Filtered cultures of the cholera vibrio have little toxic action, the virus being apparently liberated by disintegration of individual organisms. Dead cultures, given by the mouth, produce no effect, unless the intestinal epithelium is injured. The toxins are mostly destroyed at 60° C.; when ground up and frozen by liquid air, an extract of high toxicity to laboratory animals, especially when injected intravenously, is obtained. The organism multiplies in the small intestine, and liberates an endotoxin which is responsible for desquamation of the epithelium and other manifestations of the disease.

Phan was able to produce the clinical phenomena of cholera in guinea-pigs by injecting cholera endotoxin in doses of 0·05–0·1 c.c. in the neighbourhood of the splanchnic nerves. Similar results were obtained in rabbits by injecting doses of 0·2 c.c.

Methods of infection.—Infected material is conveyed from sick to healthy persons, either by water, food, or infected linen. Milk, raw fruit, vegetables and other uncooked foods are all able to serve as media for the transference of the vibrio. Clothing, if kept moist, can retain the infectivity for days and weeks. Greig has shown in India that, in stools kept in the dark at room temperatures, the average life of the vibrio is about eight days, but when dried it only survives for a few hours. In water the vibrios remain viable for a considerable time. In reservoir water they live about two weeks, but some grossly contaminated streams, such as the Ganges, are unfavourable to their survival.

Cholera carriers.—Patients who have recovered from cholera may continue to excrete the vibrio irregularly for a few weeks, but, as a rule, 90 per cent. become free from infection in 14 days and 99 per cent. in a month. The existence of apparently healthy cholera carriers has been recognized, and these may excrete vibrios for two months, though the "carrier," such as is known in typhoid, does not exist for cholera. Taylor definitely states that the convalescent and contact carriers in most cases are free from the vibrio five days from the onset of the attack or contact.

Immunity.—The guinea-pig or rabbit may easily be immunized against the cholera vibrio by repeated intraperitoneal injections of killed cultures. The serum thus obtained shows marked agglutinative properties in a high titre to cultures of the organism. Furthermore, this serum, when injected into a non-immune animal, has marked protective power against even four or five times the lethal dose. When this happens, active bacteriolysis takes place (Pfeiffer's reaction). The test is performed as follows :

A loopful of a young agar-culture of the vibrio is added to 1 c.c. of bouillon containing 0·001 c.c. of anti-cholera serum, and is injected into the peritoneal cavity of a young guinea-pig ; by means of capillary tubes inserted into the peritoneum, the peritoneal fluid is examined microscopically every few minutes. If the original culture was a true cholera vibrio, the organisms break up into globules ; if not, no change takes place. The inoculation of animals by cholera cultures produces an immune serum which is remarkable for its high agglutinating power, the titre going as high as 1 in 12,000. For an agglutination test to prove that vibrios isolated from the stools are those of true cholera, a serum of a titre of 1 in 4000 should be used.

Pathology.—Rigor mortis occurs early and persists for a considerable time. Curious movements of the limbs may take place in consequence of post-mortem muscular contractions. On dissection, the most characteristic pathological appearances in cholera are those connected with the circulation and with the intestinal tract.

If death occurred during the algid stage, the surface presents a shrunken and livid appearance. All the tissues are abnormally dry. The muscles are dark and firm ; sometimes one or more of them are ruptured—evidently from the violence of the cramps during life. The right side of the heart and the systemic veins are full of dark, thick, and imperfectly coagulated blood which tends to cling to the inner surface of the vessels. Fibrinous clots, extending into the vessels, may be found in the right heart. The lungs are usually anæmic, dry, and shrunken, occasionally congested and œdematous. The pulmonary arteries are distended with blood, the veins empty. The liver is generally loaded with blood ; the gall-bladder full of bile ; the spleen small. Like all the other serous cavities, the peritoneum contains no fluid, its surface being dry and sticky. The outer surface of the bowel has generally a diffuse rosy-red, occasionally an injected appearance. It contains a larger or smaller amount of the characteristic rice-water material, occasionally blood. The mucous membrane of the stomach and intestine is generally pinkish from congestion, or there may be irregular arborescent patches of injection here and there throughout its extent.

If death occurred during the stage of reaction, the tissues are moist ; the venous system is less congested ; the lungs are probably congested and œdematous, perhaps inflamed. Very probably there are evidences of extensive enteritis.

Greig has shown that the gall-bladder and biliary passages are frequently invaded by the cholera vibrio and that, as in enteric, this viscus may act as a reservoir of infection. Occasionally, according to the same authority, cholera may be a septicæmia ; the vibrios have sometimes been demonstrated in the substance of the lungs and kidneys, and in the spleen.

On microscopical examination of the contents of the bowel during the acute stage of the disease the cholera vibrio, in most cases, may be demonstrated. Usually it is in great abundance, occasionally in almost pure culture in the upper part of the small intestine and duodenum, but it may be very scarce in the large gut. Sections of the intestine show the vibrio lying on and between the epithelial cells of villi and glands.

Bannerjee and Dutta demonstrated focal necrosis in the kidneys with hyaline changes and sclerotic atrophy. There are also marked changes in the convoluted tubules.

Symptoms.—Although cholera may declare itself within a few hours of exposure to infection, it may also do so at any time up to ten days. Three to six days may be set down as the usual incubation period. An attack of cholera commences in one of two ways: either it may supervene in the course of what appears to be an ordinary case of diarrhœa, or it may come on suddenly, without any well-marked prodromal stage. During cholera epidemics diarrhœa is unusually prevalent. It is a common observation that at such times an attack of simple diarrhœa may, after a day or two, assume the characters of true cholera. The preliminary looseness in such cases is known as premonitory diarrhœa or cholerine and is, in fact, a mild form of cholera. Besides diarrhœa, other prodromata, such as languor, depression of spirits and noises in the ears are sometimes noted.

Description of the average case.—When true cholera sets in, profuse watery stools, usually associated with griping pains, and at first fæcal in character, pour, one after the other, from the patient. Quickly the stools lose their fæcal character, becoming colourless or, rather, like thin rice-water containing small white flocculi in suspension. Enormous quantities—pints—of this material are generally passed. Presently, vomiting, also profuse, at first perhaps of food, but very soon of the same rice-water material, supervenes. Agonizing cramps attack the extremities and abdomen; the implicated muscles stand out like rigid bars, or are thrown into lumps from the violence of the contractions. The patient may rapidly pass into a state of collapse. In consequence principally of the loss of fluid by the diarrhœa and vomiting, the soft parts shrink, the cheeks fall in, the nose becomes pinched and thin, the eyes sunken, and the skin of the fingers shrivelled like a washerwoman's. The surface of the body becomes cold, livid, and bedewed with a clammy sweat; the urine and bile are suppressed; respiration is rapid and shallow; the breath is cold, and the voice is sunk to a whisper. The pulse soon becomes thready, weak, and rapid, and then after coming and going and feebly fluttering, may disappear entirely. The surface temperature sinks several degrees below normal—to 93° or 94° F.; whilst that in the rectum may be several degrees above normal—101° to 105° F. The blood pressure is low. The systolic may register 50 mm. of mercury but is frequently unregistrable. The patient is now restless, tossing about uneasily, throwing his arms from side to side, feebly complaining of intense thirst and of a burning feeling in the chest, and racked with cramps. Although apathetic, the mind generally remains clear. In other instances the patient may wander or may pass into a comatose state.

This, the "algid stage" of cholera, may terminate in one of three ways—in death, in rapid convalescence, or in febrile reaction.

When death from collapse supervenes, it may do so at any time from two to thirty hours from the commencement of the seizure, usually in from ten to twelve. On the other hand, the gradual cessation of vomiting and purging, the re-appearance of the pulse at the wrist, the increase of blood pressure and the return of some warmth to the surface may herald convalescence. In such a case, after many hours' absence, secretion of urine returns, and in a few days the patient may be practically well again.

Usually, however, a condition known as the " stage of reaction " gradually supervenes on the algid stage.

Anuria.—The first signs of anuria are congestion of the mucous membranes and conjunctivæ, malar flush, delirium, and gradual increase in depth and rate of respiration. Recovery is marked by the passage of a few ounces of turbid, highly coloured urine and this is followed by a " critical diuresis " resembling that seen in some cases of acute glomerulonephritis.

Renal failure in cholera has been compared to anuria following crush injuries. Tomb claimed that it may be explained by the hypothesis of Freeman that collapse of the circulation, as in surgical and traumatic shock, is the result of over-stimulation of the sympathetic nervous system. This results in dilatation of the capillaries of the skeletal muscles and constriction of the dermal and abdominal vessels. It is suggested that the histological changes in the urinary tubules are due to deprivation of oxygen. The blood area is invariably raised and may reach 350 mgm. Anuria may persist for fifty hours, and the patient may yet recover.

The importance of charting the amount of urine, hour by hour, day by day, in the reactionary stage of cholera cannot be over-emphasized. These data are essential if threatened anuria is to be successfully combatted.

Reaction or cholera typhoid.—When the patient enters on this stage the surface of the body becomes warmer, the pulse returns, the face fills out, restlessness disappears, urine is secreted, and the motions diminish in number and amount, becoming bilious at the same time. Coincidently with the subsidence of the more urgent symptoms of the algid stage and this general improvement in the appearance of the patient, a febrile condition of greater or less severity may develop. Minor degrees in this reaction generally subside in a few hours ; but in more severe cases the febrile state becomes aggravated, and a condition in many respects closely resembling typhoid fever, " cholera typhoid," ensues.

During the stage of reaction death may occur from a variety of complications—from pneumonia, from enteritis and diarrhœa, from asthenia, or from such effects of uræmic poisoning as coma and convulsions.

Hyperpyrexia is an occasional, though rare, occurrence in cholera. In such cases the axillary temperature may rise to 107° F., the rectal temperature perhaps to 109° F. These cases also are almost invariably fatal.

In cholera there is a considerable variety in the character of the symptoms and in their severity, both in individual cases and in different epidemics. It is generally stated that the earlier cases are the more severe, those occurring towards the end of the epidemic being on the whole milder.

Ambulatory cases occur during all epidemics, characterized by diarrhœa and malaise merely ; there is never complete suppression of urine, the diarrhœa never loses its bilious character, and is not accompanied by cramps. The attack gradually subsides without developing a subsequent stage of reaction.

Cholera sicca.—A very fatal type is known as " cholera sicca." In these cases, though there is no, or very little, diarrhœa or vomiting, collapse sets in so rapidly that the patient is quickly overpowered as by an overwhelming dose of some poison, and dies in a few hours without purging or any attempt at reaction.

Eye changes in cholera.—Osmotic dehydration in cholera can bring about a lens opacity, which, in lesser degrees, is reversible, so far as the physical state of the water in the lens is involved.

Therefore cataract may develop suddenly in the stage of collapse and may have a similar osmotic basis to that of diabetes. In cholera loss of fluid from the bowel may lead to osmotic dilution of the body fluids, including the aqueous, and consequent inflow of water into the lens.

The ophthalmoscopic changes consist of a wavy gridiron appearance with dark lines against a red background, possibly denoting wrinkling of the capsule.

These changes disappear on rehydration.

Sequelæ are unusual. Recovery is generally complete. Occasionally there are minor sequelæ, such as anæmia, mental and physical debility, insomnia, a diphtheritic inflammation of the mucous membranes of the intestines, fauces and genitalia, nephritis, different forms of pulmonary inflammation, parotitis apt to end in abscess, ulceration of the corneæ, boils, bedsores, and gangrene of different parts of the body. Jaundice occurs at times, and is said to be of the gravest import. An interesting, but unusual, sequel is bradycardia. Pregnant women almost invariably miscarry, the fœtus showing evidences of cholera.

The prognosis of cholera is especially bad in opium addicts.

Mortality.—The average case-mortality in cholera amounts to about 50 per cent. Some epidemics are more deadly than others. As already mentioned, the mortality is greater in the earlier than in the later stages of an epidemic. To the old, the very young, the pregnant, the subjects of grave organic disease—particularly of the liver, kidneys, and heart—the dissipated, the underfed, and the feeble, the danger is very great.

Diagnosis.—During the height of an epidemic the diagnosis of cholera is generally easy; the profuse rice-water discharges, the collapse, the cold clammy skin, the cyanosis, the shrunken features, shrivelled fingers and toes, the feeble husky voice, the cold breath, the cramps, and the suppression of urine, together with the high rate of mortality, are generally sufficiently distinctive. But in the first cases of some outbreaks of diarrhœa, which may or may not turn out to be cholera, and the true nature of which, for obvious reasons, it is important to determine, correct diagnosis may not be so easy. Control measures should be applied if the clinical evidence is suggestive, without waiting for bacteriological confirmation.

In other forms of diarrhœa it is rare for the stools to be persistently so entirely devoid of biliary colouring matter as they are in cholera.

The detection of the comma vibrio in the stools is regarded as a positive indication of cholera. It would be rash, however, to affirm that a negative result from bacteriological examination of a single case rules out cholera. Moreover, such examinations, to be trustworthy, have to be made by a skilled bacteriologist.

In the first place the stools should be examined microscopically. If vibrios are present in large numbers they may be detected by their scintillating rotatory movements in hanging-drop preparations, or by their characteristic shape in fæcal films stained by carbolfuchsin. According to Koch, a rough diagnosis may be made in 50 per cent. of cases by this method. If vibrios are very numerous, plates may be spread direct by a platinum loop on alkaline agar, or on Dieudonné's medium. When the vibrios are present in small numbers—(*a*) alkaline peptone water should be inoculated with two or three loopfuls of the fluid stool and incubated for seven hours; (*b*) any pellicle present on the surface of the broth should be examined in stained films or by the hanging-drop method; (*c*) if vibrios are scanty, a second alkaline peptone tube should be reinforced by inoculation, incubating for a further six to eight hours, and plating out on alkaline agar; (*d*) an emulsion of colonies from the plate or from an agar slope sub-culture should be agglutinated against the specific antiserum in high titre.

An agglutination of over 1 in 1000 with a specially prepared serum strongly suggests the true cholera vibrio, which may then be subjected to special biochemical tests.

The full technique of identification demands a considerable amount of time, and as promptness is the first essential in cholera diagnosis, be it of acute cases or of "carriers," other methods of rapid and more or less accurate diagnosis have been devised. Such a one is Bandi's method, which consists in inoculating the suspected fæces into peptone water containing agglutinating serum of such strength as to clump the cholera bacillus in high dilution. Within as short a period as three hours' incubation, agglutination visible to the naked eye is said to be present. This method, when employed in a large number of cases, necessarily consumes a large quantity of immune serum.

The advantages of such a rapid method are several: positive reports may be obtained on a large number of cases in as short a period as eighteen hours, and as many as 200 stools may be examined by one worker during the course of a morning's work. A modification was described by Davies and the Editor. The following are the stages in the technique:

1. Inoculate a platinum loopful of fæces into peptone water, 1 per cent. peptone, 1 per cent. NaCl, made distinctly alkaline to litmus.
2. Incubate for eighteen hours.
3. Place a drop of the resulting growth on the slab of Garrow's agglutinometer (Appendix, p. 1014), together with a drop of 1 in 80 anti-cholera serum. The resulting mixture will give a dilution of cholera serum 1 in 160. On the next partition drop an equal quantity of normal saline, together with a drop of the peptone culture, to act as a control. Rotate for three minutes. If vibrios are present, a definite agglutination will be obtained. This can be confirmed later by agglutinating with cholera serum in still higher dilutions. It is recommended that stock bottles (with rubber caps) of cholera serum preserved with 0·5 per cent. carbolic acid, in dilutions 1 in 80, 1 in 160, 1 in 320, 1 in 640, be kept. If an agglutination is obtained with the lower dilutions it may subsequently be titrated with the higher ones.
4. The peptone culture can then be spread with a platinum loop on Crendiropoulo's agar (alkaline agar), and a culture obtained by this means. The cholera colonies can then easily be recognized by their transparent bluish-grey appearance. The hæmolytic and sugar tests may then be applied. It has been found that vibrios agglutinating with specific serum in high dilutions invariably give correct sugar, hæmolytic, and cholera-red reactions (p. 451).

In an autopsy on a suspected case of cholera, at least two sections of the small gut, each about 5 in. in length—one just above the ileocæcal valve, the other in the middle of the ileum—should be ligatured, cut off, dropped into sterile saline and sent to a bacteriological laboratory as soon as possible for examination.

An agglutination reaction is not obtainable from the blood-serum during the acute stage, but it is present after eight to ten days from the commencement of the disease, reaching its maximum in four weeks ; it may attain a titre of 1 in 1000.

Taylor made it plain that the question of H and O agglutinins is important in the diagnosis of cholera, as it is in other intestinal diseases of bacterial origin. The H element is present in some strains of true cholera and also in all the saprophytic water vibrios. It is affirmed that the O agglutinin is all-important. Evidence is accumulating that the O groups of vibrios are responsible for most of the serious outbreaks of cholera. Therefore, it is important that sera from cholera cases should be tested for O agglutinins.

Differential diagnosis.—True cholera may have to be differentiated from *ptomaine*, or *mushroom* poisoning, which may simulate it very closely, but in this instance there is usually a history of several persons having been attacked at the same time, after having partaken of a particular article of food, especially tinned. Leucocytosis is absent in food-poisoning though usually found during the early stages of cholera.

For the differential diagnosis of cholera from food poisoning, *see* Table VI, p. 459).

Algid or choleraic subtertian malaria may simulate true cholera very closely (*see* p. 69) ; *acute bacillary dysentery* may occasionally be so sudden and severe in its onset as to resemble cholera ; acute trichinosis is distinguished by leucocytosis and pronounced eosinophilia : in *arsenical poisoning* vomiting is more usually the most urgent commencing symptom. Children suffering from cholera are apt to develop hyperpyrexia with cerebral manifestations, which may be mistaken for meningitis.

TREATMENT

During cholera epidemics it is customary to establish depots where sedative and astringent remedies for the treatment of diarrhœa are dispensed gratuitously. Chlorodyne in small doses, 10–15 drops, has been found to be of value in allaying the more urgent primary manifestations.

In the early stages of evacuation opium is of undoubted value. A hypodermic injection of morphia, $\frac{1}{4}$ gr. with atropine gr. $\frac{1}{100}$, should be given immediately. An anti-diarrhœic of value is as follows :

℞ Sodii bicarb.	gr.xv	(0·972 grm.)
Cret. prep.	gr.xv	(0·972 grm.)
Spirit. æther.	♏xv	(0·88 c.c.)
Spirit. ammon. aromat. . . .	♏xv	(0·88 c.c.)
Tinct. opii	♏xxx	(1·77 c.c.)
Aq. chlor, ad.	℥i	(28·4 c.c.)

Of this, 1 fl. oz. should be given every twenty minutes until purging and vomiting cease.

Kaolin, or " bolus alba," as an intestinal astringent in large doses, adsorbs toxins, thus rendering them inert. It consists of kaolin[1] 200 grm.

---

[1] Kaolin powder suitable for this purpose may be obtained from the Electric Osmosis Co.

TABLE VI

	CHOLERA	FOOD POISONING
Diarrhœa.	Often associated with griping. Precedes vomiting.	Associated with some intestinal pain. Follows vomiting.
Vomiting.	Causes no distress. Watery and projectile; follows diarrhœa.	Often violent and distressing. Vomit consists of food and is never watery. Copious or projectile. *Generally precedes diarrhœa.*
Nausea.	Absent.	Constant.
Retching.	Rare.	Constant, often severe.
Abdominal pain.	Not usually severe.	Constant.
Tenesmus.	Absent.	Common.
Stools.	Watery and copious.	Liquid, fæcal, and offensive. Never colourless and copious.
Urine.	May be completely suppressed.	Never suppressed.
Muscular cramps.	Constant and severe.	In very severe cases confined to extremities.
Collapse.	Frequent. Chiefly from loss of fluid.	Faintness and syncope from toxæmia.
Fever.	Surface temperature below normal, but rectal temperature may be raised.	Axillary temperature 99–109° F.
Headache.	Absent.	Frequent.

(7 oz.) in 400 c.c. (14 oz.) of water. This is a single dose, but if there is vomiting it may be repeated, and sipped in small amounts at a time. It is inconvenient to administer on a large scale, on account of the bulkiness of the dose.

It has been shown that the adsorption-rate by kaolin is much more rapid in the case of the cholera vibrio than with an emulsion of equal strength of typhoid. Rapid adsorption is one of the reasons why kaolin in massive doses is beneficial in the treatment of cholera.

Subsidiary measures.—The patient should be kept strictly in the horizontal position, in a warm bed, and in a well-ventilated, but not too cold room. Thirst should be treated by sips of iced water, soda-water, champagne, or brandy and water. Copious draughts, as they are likely to provoke vomiting, are usually condemned. It does not follow from this that they are harmful; the emesis contributes to the elimination of toxins.

Cramps may be relieved by gentle frictions with the hand, by a small hypodermic injection of morphia, or, these failing, by chloroform inhalations.

The surface heat is maintained by hot-water bottles or warmed bricks placed about the feet, legs, and flanks. The patient must not be allowed to get up to pass his stools; a warmed bed-pan should be provided for this purpose. The foot of the bed should be raised. All food should be withheld while the disease is active.

Intravenous salines.—For the stage of collapse, which is due to the loss of a large amount of fluid, intravenous injections of salines must be resorted to in order to restore the balance. Collapse in cholera does not differ fundamentally from that due to hæmorrhage, and similar principles of treatment underlie both. Intravenous injection of normal saline is therefore indicated, but success appears to depend on the introduction of a sufficient quantity. Three to four pints may be necessary. Cox of Shanghai had encouraging results from continuous, prolonged, slow intravenous injections of isotonic saline fluid given by a special apparatus placed 2½ ft. above the level of the patient's arm. The flow is kept up for several hours, at a rate of 2 oz. per minute, as long as there is danger from collapse.* The saline injections may be combined with 5 per cent. glucose, which may act beneficially in urinary suppression. Normal saline was preferred as a routine in Hong Kong, because hypertonic salines were not successful. Ride (1938) considered that, until the nature of the fluid loss in cholera has been ascertained, it is better and more scientific to make good the dehydration loss by normal saline infusions. Recent experiences indicate that intravenous injections of plasma (or reconstituted plasma), in addition to normal saline, are physiological and beneficial. Should the veins be difficult to penetrate, transfusion may be performed into the peritoneum or under the breast. After introduction of two to four pints of saline into the peritoneal cavity, the veins soon become prominent, and intravenous injection can then be carried out.

Treatment of hyperpyrexia.—During the saline infusion, half-hourly charts of the rectal temperature should be kept and, should hyperpyrexia supervene, ice-packs must be applied and iced injected *per rectum.*

Rogers's treatment.—Though modern therapeutists regard this method as being based upon faulty physiological reasoning, it is necessary to give an outline of the data. Rogers, believing that collapse in cholera was due to excessive loss of chlorides from the blood-stream, introduced the intravenous *hypertonic* saline treatment. This is composed as follows: sodium chloride, 120 gr.; potassium chloride, 6 gr.; calcium chloride, 4 gr.; sterilized water, 1 pint. The fluid in the containing bottle should be at a temperature of about 100° F. if the rectal temperature is below 99° F.; if the latter is above 100° F., as there is risk from hyperpyrexia, the injection should be given at a temperature between 80° and 90° F. This solution is introduced by means of a special stopcock cannula and transfusion bulb at the rate of not more than 4 oz. a minute, the flow being slowed down to 1 oz. if distress or headache supervenes. From three to six pints should be run in, if possible. On an average, fifteen minutes should be taken for two pints of fluid. At the same time, potassium permanganate in solution or in pill by mouth up to 50 gr. a day is given in order to destroy toxins formed in the alimentary canal—2 gr. every quarter of an hour for two hours, then every half-hour until the stools are coloured green. These pills are made up in some inert material, such as kaolin and vaseline, without the addition of any oxidizable substance. They are coated with salol, in the proportion of one part to five parts of sandarach varnish.

With intravenous saline Rogers combined hypodermic injections of atropine, $\frac{1}{100}$ gr., morning and evening. The principles of the treatment are as follows:

A blood-pressure below 70 mm. of mercury indicates a dangerous collapse, and a specific gravity of the blood of 1063 or over indicates a loss of half the fluid from the blood. In the acute stage the specific gravity of the blood varies between 1060 and 1072, the normal figure for a European adult being 1058 and for an Eastern native 1056.

The specific gravity of the blood is estimated by employing a series of small bottles of aqueous glycerin with specific gravities increasing by 2° per bottle from 1048 to 1070. The specific gravity may be controlled by a urinometer. Blood from the patient is dropped on to the surface of the fluid in the bottles by a capillary pipette. The drop which remains stationary in the centre of the glycerin solution of a given strength indicates its specific gravity.

In the stage of collapse, anuria often occurs, and every effort must be maintained to re-establish the blood-pressure. Pituitary extract, or pitressin, is often useful during the stage of reaction, given in doses of $\frac{1}{2}$ to 1 c.c., hypodermically, two to four times a day; adrenalin may also be given, but its action is more transient. Caffeine citrate, 5 gr., is useful as a cardiac tonic and as a diuretic; it may be given three or four times during the twenty-four hours. Tincture of strophanthus, 5 min., three times a day, is useful as an adjuvant. In cases of complete suppression, dry-cupping over the lumbar region twice daily by Fenwick's cups may help to re-start the flow of urine, and may be supplemented later by hot dry fomentations. Rectal injections of hyperalkaline saline—150 gr. of sodium bicarbonate to the pint of isotonic saline—should be administered slowly every 2–4 hours in cases where collapse has been overcome but suppression of urine persists. The objection to using sodium bicarbonate is that this salt has a lytic action on the red cells *in vitro*, but in 4·5 per cent. concentration it has no hæmolysing effect. During sterilization the bicarbonate tends to be converted into the carbonate, but Sellards found that this tendency was minimized by sterilization in an autoclave connected with live steam at 7-lb. pressure.

If the secretion of urine is not quickly restored, large hot poultices or dry-cupping over the loins, and the judicious use of bland diuretics should be tried. Injections of digitalin, $\frac{1}{100}$ gr., may be given to stimulate the cardiac action.

During the stage of reaction, should purging persist, large doses of salicylate of bismuth with a little opium may prove of service.

Cholera typhoid must be treated much as ordinary enteric fever.

In cholera convalescents the diet for a time must be of the simplest and most digestible character—diluted milk, barley-water or rice-water, thin broths, meat juice, and so forth—the return to ordinary food being effected with the greatest circumspection.

Essential oils.—A popular treatment in India is an essential-oils mixture as follows:

℞ Spirit. æther.	♏xxx	(1·176 c.c.)
Ol. anis.	♏v	(0·296 c.c.)
Ol. cajup.	♏v	(0·296 c.c.)
Ol. junip.	♏v	(0·296 c.c.)
Acid. sulph. aromat.	♏xv	(0·888 c.c.)

Half a drachm (1·176 c.c.) in half an ounce of water, every quarter of an hour Total dose, 8–14 drachms.

This mixture should be given immediately, when practicable, and it is claimed that vomiting, purging, and intestinal pains are controlled. The value of the method in mass treatment is obvious, as little supervision is requisite.

Sulphaguanidine.—Chopra and colleagues first reported on this treatment in cholera. The dosage to an average Indian patient in this series was 5 grm. on admission, and 2·5 grm. every four hours until a total of 20 grm. had been given. The mortality rate was 3·21 per cent. Others have not found sulphaguanidine of any value, even when combined with intravenous hypertonic saline.

Bacteriophage.—Asheshov, Khan, and Lahiri gave bacteriophage together with intravenous hypertonic saline. Sterilization is done under pressure in the autoclave (30 minutes at 120° C.) and not by boiling. Three pints of hypertonic saline are given intravenously, together with an additional pint of alkaline salt solution (150 gr. sodii bicarb. to a pint of normal saline). Together with this the cholera bacteriophage is given undiluted by the mouth in one drachm doses every 30 minutes, or 5 c.c. intravenously for more rapid action. The results have not been impressive.

Anticholera serum.—Ghosh and others tried injection of a new anticholera serum of an increased potency. This has been produced by a modification of toxin production with the object of obtaining a maximum quantity of both endo- and exotoxin. The serum is best injected intraperitoneally in doses of 70–80 c.c. The results are stated to be encouraging, and it was found that, in cases with a blood specific gravity of 1064 or more, the mortality was reduced by more than 50 per cent. No cases of uræmia occurred in the series. The intravenous injection of the serum is by no means so favourable as the intraperitoneal.

Mortality-rate.—The death-rate for cholera has always been high. In former days in India it was seldom less than 70 per cent. In the decade ending 1908 it was 54·2 per cent. in Indian and 78·5 per cent. in British troops in India. With improved methods of treatment it has declined, but is still about 20 to 30 per cent. The death rate in collapsed cases is considerably higher, and, even with modern methods, remains about 65 per cent.

The prognosis is unfavourable in those over fifty years of age and in children under five.

Prophylaxis. *Quarantine prevention.*—Theoretically, quarantine should be an efficient protection against the introduction of cholera into a community; practically, it has proved difficult to apply. Unless they are stringent and thoroughly carried out, these regulations can be of little use. Even if the utmost care, intelligence, and honesty succeed in excluding individuals actually suffering from cholera, or likely within a reasonable time to suffer from it, there is yet no guarantee that the germ of the disease may not be introduced. Convalescent patients may pass vibrios in their stools. For the recognition of the carrier state it is necessary to examine the stools of all contacts. A small dose of calomel to clear out the contents of the small intestine greatly increases the chance of recovering the specific organism from stools. This is the only scientific method of conducting a reliable quarantine.

The system to which Great Britain apparently owed her immunity during epidemics on the continent of Europe is a practicable and, in civilized conditions, an efficient one. Under this system, only ships which were carrying or which had recently carried cholera patients were detained; and even these merely until they could be thoroughly disinfected. Thus, inconvenience and loss to travellers and merchants were small, and the temptation to conceal cases of the disease or to evade regulations was proportionately minimized. Any cholera cases were isolated in suitable hospitals, the rest of the crew and passengers, although supervised for a time, being given free pratique. At the same time attention was not diverted from the sanitation of towns, especially of seaports—the measure mainly relied upon. Suspicious cases occurring on shore were at once reported to the sanitary authorities and promptly dealt with, fomites being destroyed or disinfected at as little cost and inconvenience to individuals as possible. Every endeavour was made to prevent fæcal contamination of the public water supply.

Of late years, in India, preventive measures have been conducted much on the same lines, attention being given to sanitation rather than to quarantine. During the great religious festivals the sanitary condition of the devotees is looked after as far as practicable, special care being given to provide them with good drinking and bathing water. On the appearance of cholera in the vicinity of troops in India, special protective measures are promptly instituted, elaborate directions having been drawn up for the guidance of medical officers.

Wells and water supplies during a cholera epidemic should be treated with potassium permanganate until the water becomes pink; an appropriate strength is 60 gr. to the gallon of water. The water should not be used until it has been colourless for twenty-four hours, and all vegetation and aquatic fauna removed.

It is held in India that one of the major measures of prevention is the provision of safe permanent water supplies to the whole population.

The application of bacteriophagic principles to sanitation.—According to Graham and Morison, cholераphage is absent in the intestinal tract before the beginning of a cholera epidemic. Little or no phage is found in the first victims to be stricken, and this substance is elaborated as the epidemic progresses, so that those patients who develop a rapid exaltation of choleraphage recover. Thus, this factor can be used as a prophylactic measure in disinfecting wells. For this purpose 30 c.c. of potent bacteriophage were added to two wells in the contaminated area. One case only developed in those who drank this water.

Haffkine's inoculation.—During the 1914–1918 war many millions of anticholeraic inoculations were made. The initial dose is ½ c.c. of an emulsion of 4,000 millions, followed seven to ten days later by a second inoculation of 1 c.c. containing 8,000 millions. Experience has shown that even larger doses can easily be tolerated. Local reaction is, generally speaking, very mild. There may be œdema and a painful infiltration at the site of the injection, rarely followed by systemic disturbance.

Several strains of cholera vibrios are used. They are inoculated into Roux bottles containing "pea-extract agar" and grown for forty-eight hours. The growth is washed off with normal saline, and the emulsion counted, with dark ground illumination. The emulsion is then heated to 55° C. for one hour, after which 1 per cent. carbolic is added. The emulsion thus sterilized is finally diluted down so as to contain 8,000 million vibrios per c.c. of saline and 0·5 per cent. carbolic.

The immunity thus produced does not seem to be very persistent, lasting at the maximum for three or four months.

Experience, particularly that obtained during the Balkan War in 1913, in Batavia in 1915 and 1916, and in the 1914–18 war, has gone far to confirm the earlier impressions of the value of Haffkine's inoculation.

In India from 1905–1916 the annual number of deaths attributed to cholera was never less than 300,000. Epidemics of cholera are readily controlled by vaccine when inoculation is made compulsory; thus, when this disease was introduced into Korea from China in 1926, the outbreak was promptly brought to a close by the inoculation of more than one million persons.

Immunization per os.—(Besredka). The vaccine is made from thick suspensions of the organisms killed by heat, carbolic acid, or alcohol, and given in from 3 to 5 doses ranging up to 100 c.c. every other day. Each dose consists of 10–100 milliards of vibrios, or 0·01–0·1 grm. of the dried organisms. The full course of bili-vaccine, as it is called, is said to confer the same degree of immunity as ordinary vaccine, but that produced by a simple inoculation is probably as high as that afforded by a full course of bili-vaccine.

Personal prophylaxis.—During cholera epidemics great care should be exercised to preserve the general health; at the same time, anything like panic or apprehension must be sedulously discouraged. Visits to cholera districts should be postponed, if possible, seeing that the newcomer is especially liable to the disease. Unripe fruit, over-ripe fruit, shell-fish and food in a state of decomposition should be avoided. All drinking-water, and all water in which dishes and everything used in the preparation and serving of food are washed, should be boiled. Mere chlorination of the water with bleaching powder ($CaOCl_2$), giving 1·3 parts of chlorine per million, or added to water in the proportion of 2 grm. of the powder to every 110 gallons, is not entirely reliable. Sodium bisulphate tablets (2 grm. to 1¾ pints of water), by liberating sulphuric acid, provide a most useful method of sterilizing water for personal use, as for instance in a water-bottle. Filters—except perhaps the Pasteur-Chamberland—are not for the most part to be relied upon; in many instances they are more likely to contaminate the water passed through them than to purify it. A good plan in a household or in public institutions is to provide for drinking purposes an abundant supply of weak tea or lemon decoction, the supply being renewed daily; such a plan ensures that the water used in the preparation of the drink has been boiled. All food should be protected from flies. Diarrhœa occurring during cholera epidemics should be vigorously treated.

CHAPTER XXVIII

THE DYSENTERIES AND LIVER ABSCESS

THREE types of dysentery, correlated to three quite distinct and, zoologically, widely separated parasites have now been definitely established. Though of a totally different ætiology they are not mutually exclusive, for one type may be superimposed upon and complicate another; moreover, any or all of them may be implanted on some general disease, such as malaria or typhoid. The term "dysentery" denotes a symptom-complex, but does not indicate some particular disease of distinct ætiology. It is most important that a sane and critical view should be taken on the all-important matter of differential diagnosis of the dysenteries as there are many pathological conditions of the intestines which may give rise to a discharge of blood and mucus, but which are not connected with any particular parasitic infection.

The principal forms of dysentery and their respective parasites are as follows:

- I. BACTERIAL—
  - THE BACILLARY DYSENTERIES:
    - *Bacterium dysenteriæ*—Shiga, Schmitz, Flexner and Sonne.
- II. PROTOZOAL—
  - AMŒBIASIS—Amœbic dysentery, Liver abscess, etc.
    - *Entamœba histolytica.*
  - BALANTIDIAL DYSENTERY:
    - *Balantidium coli.*
- III. HELMINTHIC—
  - BILHARZIAL DYSENTERY:
    - *Bilharzia mansoni*, *B. hæmatobia*, *B. japonica.*
  - VERMINOUS DYSENTERY:
    - *Œsophagostomum apiostomum*, or *Œ. stephanostomum.*

I. BACILLARY OR EPIDEMIC DYSENTERIES

EKIRI—Japanese

Definition.—Acute epidemic diseases due to invasion of the mucosa of the large intestine by specific bacilli (*B. dysenteriæ* Shiga, Schmitz, Flexner, or Sonne). Pyrexia, symptoms of toxic absorption, and the discharge of blood-stained mucus in the stool usually occur. In severe cases coagulation necrosis of the mucosa may take place and quickly lead to death. In the milder forms the clinical symptom may be a simple diarrhœa.

Geographical distribution.—Epidemics of bacillary dysentery are frequent both in the tropics and in temperate countries. At present such epidemics are of greater intensity and frequency in those countries in which the insanitary habits of the natives and more primitive conditions of life lend themselves to the spread of disease. In mediæval times bacillary dysentery epidemics seem to have been much more widespread and virulent when the sanitary conditions were more akin to those among primitive tropical natives. In Europe, bacillary dysentery is mainly an institutional disease, occurring not infrequently in lunatic asylums, prison camps, and military barracks. In the Gallipoli campaign (1915) it was responsible for the majority of the 120,000 medical casualties evacuated within three months. Sonne dysentery has been widespread, especially in children, during recent years, during the winter months, in England, Europe and America.

Epidemiology.—In the tropics and subtropics, the bacillary dysenteries appear to observe a definite seasonal incidence. They are certainly prevalent during the rainy season and for a short subsequent period, but mostly in the autumn months, while minor epidemics may also be noted in the early spring. During the hot dry African summer they are in abeyance. Epidemic dysentery is associated with the rainy season in the tropics for the following reasons. The rains deter people from defæcating at a safe distance from the village; waterlogging of the soil prevents the bacilli from dying out; people are more liable to chills, which often cause an acute attack; natives crowd together, which increases the chances of infection, together with an increased risk of pollution of water supplies. The infection spreads rapidly from man to man.

Bacillary dysentery has always been a scourge of war. If we may trust the records of history it was an important factor in the Napoleonic wars, in the Franco-Prussian War of 1871, and in the South African War of 1899–1902. Large epidemics of bacillary dysentery occurred during the war of 1914–18, and as a cause of invaliding it was hardly secondary to any other disease. In the Middle East, India, Iraq and East Africa the general tendency was to mistake, for reasons pointed out on p. 478, amœbic for bacillary dysentery. That bacillary dysentery was the predominating form in every epidemic of war dysentery from the Gallipoli campaign onwards was pointed out by the Editor and others. This has been borne out by the experience of the present war.

Direct contagion by fæces occurs, as a rule, among primitive communities in which the ordinary sanitary observances are either unknown or disregarded. The spread of dysenteries in lunatic asylums and Indian bazaars is attributable to personal habits which lend themselves to dissemination of infection. Contamination of food by the soiled hands of carriers, especially Army cooks, and contamination of vegetables by use of human nightsoil as a fertilizer are also possibilities.

Indirect contagion. (*a*) *Flies.*—There appears to be little doubt that houseflies (*Musca domestica*) commonly act as carriers of the infection. The seasonal incidence of bacillary dysentery corresponds in a remarkable manner with the maximum prevalence of these pests. In 1910 the Editor demonstrated Shiga dysentery bacilli, in considerable numbers, in the intestinal tract of houseflies in an endemic area. This work was confirmed by Taylor and others. The housefly is able to spread dysenteric infection firstly, by regurgitation preparatory to feeding on food; and secondly (probably more commonly) by its fæces. Buxton found that the intestinal canal of the majority of houseflies caught in Iraq contained human fæces.

The importance of the insect in the spread of the bacillary dysenteries can therefore be understood.

(*b*) *Water* acts as a medium of infection, especially in the Dutch East Indies and Malay States. It has been shown that the bacillus can survive in drinking-water for over three weeks, but not for so long when exposed to the sun or when associated with numbers of putrefactive micro-organisms.

(*c*) *Milk.*—Several outbreaks of Flexner and Sonne dysentery in southern England and in Europe have been ascribed to contaminated milk.

(*d*) *Food.*—Sonne dysentery is a food infection and should be classified among the group of food-poisonings. One of the largest outbreaks in London in 1933 was ascribed to eating " pease pudding."

(*e*) *Susceptibility of the individual.*—New arrivals in the tropics are liable to this form of dysentery, and small children are specially so. Patients whose resistance has been undermined by intercurrent disease, such as malaria, pellagra and tuberculosis, are apt to die from terminal bacillary dysentery.

(*f*) *Carriers* (*see* p. 477).

Ætiology.—*Bact. dysenteriæ* was discovered by Shiga in 1898, confirmed two years later by Kruse in Germany. It has therefore been known as the Shiga-Kruse bacillus.

Shiga's bacillus is a rod-shaped Gram-negative organism, 1 to 3 μ in length by 0·4 μ in breadth ; it is non-motile, and often exhibits very active Brownian movement. Vedder and Duval have demonstrated numerous lateral flagella of great tenuity. On agar and gelatin it grows as a thin smooth film with regular margins, and on MacConkey plates its colonies much resemble those of the typhoid bacillus ; they are regularly round, light-blue and dew-like. It produces no liquefaction of gelatin, and grows as a transparent, almost invisible, layer on potato. With solutions of the sugars (*see* Table VII, p. 468) it produces acidity in glucose, but is inert in the rest of the series and does not produce indol in peptone water. The organism is agglutinated in high dilutions by the serum of patients suffering from the disease. It occurs in considerable numbers in dysenteric lesions, and in the mucous stools of the corresponding period of the disease.

A variety of Shiga's bacillus (resembling that organism in its sugar reaction, *but forming indol* and not agglutinating with Shiga-immune serum) is known as Schmitz's bacillus and has been shown to be of considerable importance in the Middle East. (This organism is identical with *B. ambiguum* of Andrewes.)

Cultures of *Bact. shigæ* are toxic to laboratory animals, especially rabbits, but in these animals they do not produce lesions characteristic of dysentery, though filtered toxins, when injected intravenously, cause necrosis of the large intestine. In two experiments in man, one intentional, the other accidental, ingestion of pure cultures was followed, within a short time, by well-marked symptoms of dysentery.

Flexner's bacillus **(the Flexner-Boyd group).—In 1900 an organism morphologically similar to Shiga's bacillus, but differing in the production of acid from mannite as well as glucose, producing indol from peptone somewhat irregularly, and inagglutinable with Shiga-immune serums, was isolated by Flexner from cases of dysentery in Manila. From the work of Andrews and Inman on a very large number of strains of Flexner—*the mannite-fermenting group*—it can be definitely stated that the organism does not adhere to one constant type, as does Shiga's bacillus, but differs greatly in the toxicity of the various strains and in their**

TABLE VII.—BIOLOGICAL REACTIONS OF PATHOGENIC AND ALLIED ORGANISMS RECOVERED FROM THE FÆCES

	Mannite		Glucose		Maltose		Lactose		Saccharose		Dulcite		Litmus or Phenol Red Milk			Indole	Motility
	A	G	A	G	A	G	A	G	A	G	A	G	A	Alk	Clot		
Bact. shigæ . . .	0	0	+	0	0	0	0	0	0	0	0	0	+	0	0	0	0
Bact. flexneri . . .	+	0	+	0	+	0	0	0	0	0	0	0	+	+	0	+	0
Bact. ambiguum (Schmitz's bacillus) . . .	0	0	+	0	0	0	0	0	0	0	0	0	+sl	0	0	+	0
Bact. Sonnei . . .	+	0	+	0	0	0	+	0	+ or 0	0	0	0	+	0	+	0	0
Newcastle bacillus . .	±	0	+	+sl	+	—	—	—	—	—	+	—	+	+sl later	—	—	+
Bact. morgani . . .	0	0	+	+sl	0	0	0	0	0	0	0	0	0	+	0	+	+
Bact. typhosum . .	+	0	+	0	+	0	0	0	0	0	0	0	+	0	0	0	+
Bact. paratyphosum A. .	+	+	+	+	+	+	0	0	0	0	+	+	+	0	0	0	+
* *Bact. paratyphosum B.* . .	+	+	+	+	+	+	0	0	0	0	+	+	+	+	0	0	+
* *Bact. enteritidis* . .	+	+	+	+	+	+	0	0	0	0	+	+	+sl	+	0	0	+
Bact. coli . . .	+	+	+	+	+	+	+	+	0	0	+	+	+	0	+	+	+
Bact. acidi lactici (Hüppe) .	+	+	+	+	+	+	+	+	0	0	0	0	+	0	+	+	0
Bact. fæcalis alkaligenes .	0	0	0	0	0	0	0	0	0	0	0	0	0	+	0	0	+

A = acid. G = gas, Alk = alkaline, Sl = slight.

* To differentiate *Bact. enteritidis* and other organisms of the food-poisoning group from *Bact. paratyphosum B.* serological tests must be applied.

antigenic properties. The basis for satisfactory sub-grouping was established by the serological method of Murray, Andrewes and Inmân. It appeared that five definite strains of the bacillus could be identified, known respectively as V, W, X, Y, Z, and for their recognition five specially prepared homologous serums were necessary. The more recent study (Boyd, 1938) of antigenic variation among mannite-fermenting dysentery bacilli suggests that loss in culture of *type-specific* antigen, which is not shared by other members of the group, is associated with an increase, real or apparent, of non-specific *group* antigen. A different explanation of the observations of Andrews and Inman is thus put forward. It seems probable that available cultures of the historical Hiss and Russell Y are degenerate variants of an original W strain, and that an Indian strain, 103A, is actually the type-specific Flexner-Y. This has been found to be fairly common, both in the United Kingdom and in other parts of the world (W. M. Scott, quoted by Boyd). This work emphasizes the great importance of using type-specific suspensions in diagnostic agglutination tests. Stock Flexner-Y strains may on these grounds be almost or quite devoid of type-specific antigen.

The Newcastle bacillus, first recognized as a cause of dysentery by Clayton and Warren, corresponds to Boyd's No. 88. It has now been found in other parts of England, India and Nigeria. Owing to the fact that it forms small quantities of gas in solution of the sugars and is motile on first isolation, it frequently escapes detection.

Sonne's bacillus (*Bacterium dysenteriæ sonnei*) which ferments lactose slowly, is responsible for outbreaks of enterocolitis in Egypt and elsewhere (Perry), and may produce symptoms of food poisoning resembling those of the *Salmonella* group. The importance of this infection has been recognized in England and in America during recent years as a cause of dysentery and diarrhœa of definite seasonal occurrence, especially in children. The colonies of this bacillus tend to assume a much more crenated outline than do those of the Flexner type, but are usually larger than those of Shiga or Flexner on MacConkey's medium. Cultures of Sonne's bacillus are not agglutinated by standard Flexner or Shiga sera. When titrated against a specially prepared Sonne anti-serum, agglutination to full titre occurs. Often, however, when freshly isolated, the bacillary emulsion is inagglutinable, but will abstract the agglutinins from Sonne serum by absorption. On MacConkey's medium, Sonne colonies frequently show a small central point of acidity on a somewhat opaque background. Sonne's bacillus is indol-negative and zylose-negative. It ferments glucose and mannite in twenty-four hours, and lactose and saccharose after some days. Serological varieties and strains are now recognized. Though not so toxic as Shiga's bacillus, Sonne's bacillus, when injected into rabbits, may produce sudden death.

Dysentery bacilli can be isolated from the intestinal canal and the mesenteric glands. The organisms have also rarely been obtained from the blood-stream, gall-bladder and joint-effusions. Selective cultivation media, especially for Flexner and Sonne bacilli, have been introduced to render their isolation easier. The best is Leifson's desoxycholate-citrate medium (Haynes' modification).

Apparently both the Shiga and Flexner bacilli are encountered in sporadic cases and in some epidemics without a preponderance of any one particular type ; but it may be stated that Shiga's bacillus is more frequent in the tropics than in temperate zones, and is responsible for the most severe clinical forms of the disease, and consequently for the most virulent epidemics.

Toxins.—The O forms of *Bact. shigæ* contain both exo- and endotoxins. The former is insoluble in dilute trichloracetic acid, whilst the endotoxin can be precipitated from watery solution by means of alcohol or acetone, after removal of the acid by dialysis, yielding 10 per cent. of dry weight of the organisms. There are said to be two endotoxin fractions which are distinguishable by their nitrogen content and toxicity. Adsorption is effected by aluminium hydroxide. The endotoxin appears to be a large molecule complex of phospholipoid-carbohydrate-polypeptide. The chemical properties of the exotoxin are those of a protein. It is thermolabile and its capacity to combine with antitoxin can be measured by its flocculation reaction. Formalized toxoid can be prepared from it, but not from the endotoxin. Exotoxin can be concentrated by ammonium sulphate fractionation. The properties of different dysentery toxin preparations depend upon origin, strains and methods of preparation (Wagner-Jauregg and Helmert, 1942).

Pathology.—The primary lesions of bacillary dysentery (Shiga and Flexner infections) are confined to the solitary follicles of the large intestine, and result in a sinuous " snail-track " ulceration of the folds of mucous membrane. In very acute cases the process consists of intense hyperæmia of the large intestine, which eventually culminates in necrosis of the mucosa of the entire colon, as well as of the last 2–3 ft. of the ileum. Exceptionally, the whole of the mucosa of the small intestine may be involved.

As a general rule, the lesions characteristic of bacillary dysentery are most pronounced in the lower part of the intestinal canal, from the sigmoid flexure to the anal canal. In the stage of *necrosis* the large gut is contracted so as to resemble a stiff tube, and the mucous membrane is converted into a rigid, resistant, olive-green or blackish substance (Plate X, Fig. 3). The colour is thought to be due to the staining of the dead tissue by bile-pigments. Occasionally, this necrosis may have a patchy distribution affecting especially the descending and pelvic portions. There are many signs of acute toxæmia.

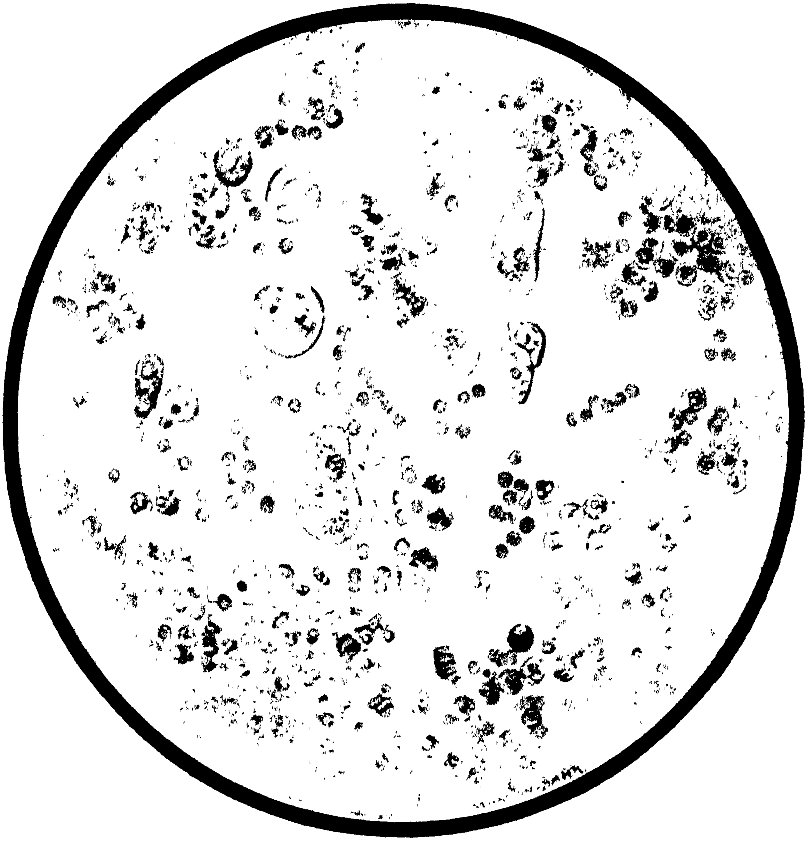
When the necrotic patches have a more local distribution, irregular ulcers, often communicating with one another by submucous sinuses, form and may involve the entire wall; such a bowel surface has a fenestrated appearance. Inflammatory changes are found in the mesenteric glands, with macrophage activity.

Chronic ulceration of the large gut may occur in bacillary dysentery. The smallest lesions are lenticular and involve the mucous surface alone. The more advanced lesions amount to ulceration of limited tracts of mucous membrane, rarely penetrating beneath the muscularis mucosæ. Ante-mortem perforation of the gut may supervene, though it is rare. For the differentiation of these ulcers from those of amœbic dysentery the reader is referred to Table VIII, p. 481.

These ulcers must also be distinguished from those of tuberculous, typhoid, or bilharzial origin, and also of ulcerative colitis. In some chronic cases the mucous membrane may be entirely destroyed, rendering recovery impossible. The gut then resembles a piece of chamois-leather with interlacing fibrotic strands on the surface.

Mucous retention cysts, due to the formation of pseudo-adenomata from the bases of Lieberkühn's follicles, may sometimes be found as a sequela of bacillary ulceration, as first described by the Editor. They may be recognized as jelly-like elevations forcing up the mucous surface and scattered throughout the length of the large gut. Dysentery bacilli may be isolated from their contents, and they are present in the large intestine of " carriers " of bacillary dysentery (Fletcher and Jepps.

Granulation tissue.—Many cases of chronic bacillary dysentery acquired in the 1914–18 war showed no ulceration, but a granular condition of the mucous membrane of the large gut. The lesions are distributed, as a rule, irregularly, usually confined to the lower portion. Considerable infiltration of the walls of the gut is associated with this condition. As in ulcerative colitis, stenosis of the



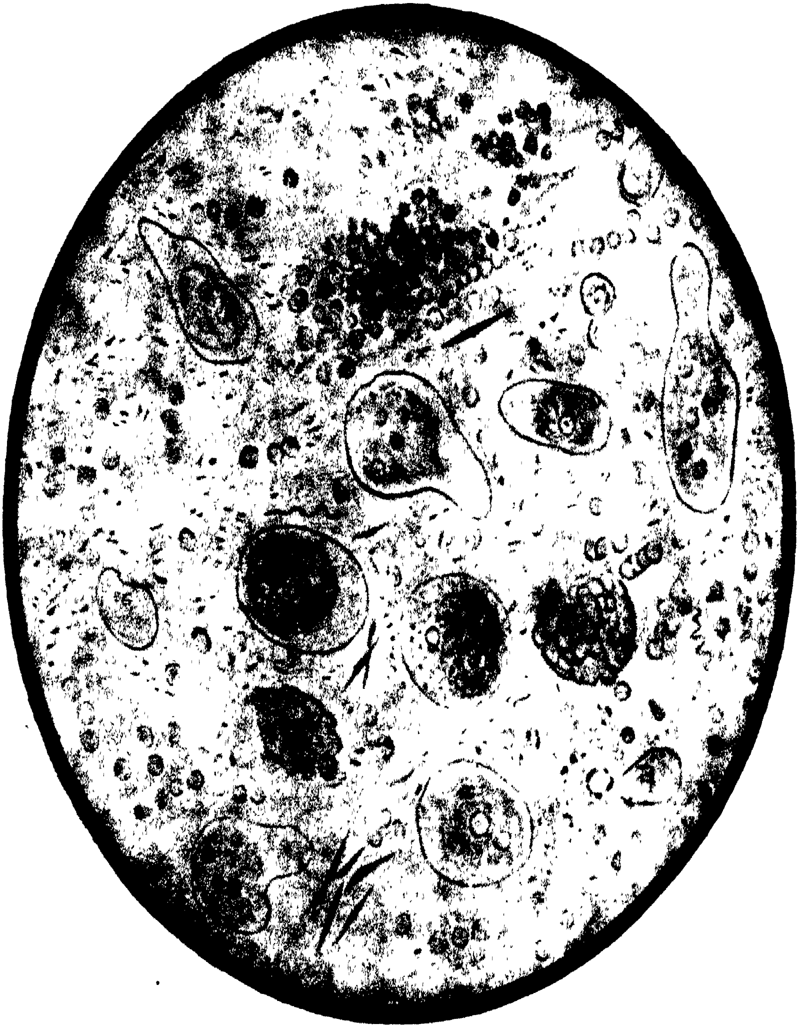
(P. H. Manson-Bahr, del.)

MICROSCOPIC APPEARANCE OF CELLULAR EXUDATE IN ACUTE BACILLARY DYSENTERY (Shiga infection).

Fresh preparation. Shows macrophage cells with ingested red blood-corpuscles, intestinal epithelium and polymorphonuclear leucocytes.

PLATE XI

WAB SALAR JUNG BAHADUR



(*P. H. Manson-Bahr, del.*)

MICROSCOPIC APPEARANCE OF EXUDATE IN AMŒBIC DYSENTERY.

Fresh preparation. Shows active *Entamœba histolytica,* some with ingested red blood-corpuscles; acicular Charcot-Leyden crystals and disintegrated intestinal epithelium.

PLATE XII

large intestine, either localized or general, may take place as a result. Mixed infection of amœbic and bacillary dysentery may be sometimes met. The spleen shows congestion of pulp and reticulo-endothelial activity. The kidneys in Shiga infections may show patchy glomerular congestion and catarrhal changes. In cases of longer duration the kidneys are enlarged and the convoluted tubules necrosed, with extensive cloudy swelling. Nephritis is often the cause of death (Dick, 1942). Emboli in liver and spleen occur.

Histopathology.—The submucosa is the seat of numerous hæmorrhages and of round cell-infiltration (Fig. 66). The ganglion cells of Auerbach's plexus are involved in perilymphatic inflammation. The formation of macrophage cells from the capillary endothelium of the vessels may also be observed. Owing to their large size, hyaline appearance, and vacuolated protoplasm, these cells, even in microscopic sections, are apt to be mistaken for *Entamœba histolytica* (Plate XI). These cells appear in an early stage in acute ulcers and in granulation tissue of chronic lesions.

The pathological appearances of Sonne dysentery are not so well known as are those of Shiga and Flexner infections. The changes are, on the whole, similar, but not by any means so severe (Plate X, Fig. 2).

Symptoms.—After a short incubation period, usually of from one to seven days (as ascertained by experiment) the disease begins in a variety of ways, suddenly or insidiously, in all degrees of severity from mild diarrhœa to an acute fulminating attack.

The main clinical symptoms are those of inflammation of the large intestine, viz., griping, tenesmus, frequent passage of loose, scanty, muco-sanguineous stools, often with dysuria.

The onset may be attended with high or moderate fever, or there may be no rise of temperature. The symptoms may be grafted on to some general disease such as scurvy or malaria, or to some chronic disease of the alimentary canal, as sprue; they may assume acute characters, or they may be subdued from the outset. As a general rule, the closer to the rectum the lesions are placed the more urgent the tenesmus; the nearer the cæcum the more urgent the griping. General constitutional symptoms due to the absorption of toxins may be evident. Vomiting may occur from the outset or be absent altogether.

Palpation of the abdomen is difficult during the early stages, owing to the rigidity of the recti muscles. Later, especially in toxic cases, the abdomen may become quite lax and the spastic sigmoid colon can be felt as an elastic cord. Implication of other portions of the large intestine can usually be detected from tenderness on pressure.

Blood changes.—There are few characteristic blood changes. As a rule, there is a polymorphonuclear leucocytosis of 16,000–30,000 at the commencement of the attack, falling to normal or subnormal on the third or fourth day.

Character of the stools.—At first fæcal and diarrhœic, the evacuations may vary enormously in number and character. Their number may be uncountable, the unfortunate victim being " glued to the commode." At first they consist of viscid blood-stained mucus, which has been compared to " red-currant jelly " or " frog's spawn," and are generally odourless. The characters by which they may be distinguished from amœbic fæces are given on p. 481. A few teaspoonfuls only may be passed at a time.

Subsequently they contain less blood and become more purulent. Finally, biliary pigments re-appear and the fæcal character may be re-established.

In the most acute and fulminating forms the mucus may contain a large proportion of altered blood and the evacuations resemble " meat washings." When necrosis of the mucosa has taken place the stools may be exceedingly offensive, grey, and contain much altered blood without mucus.

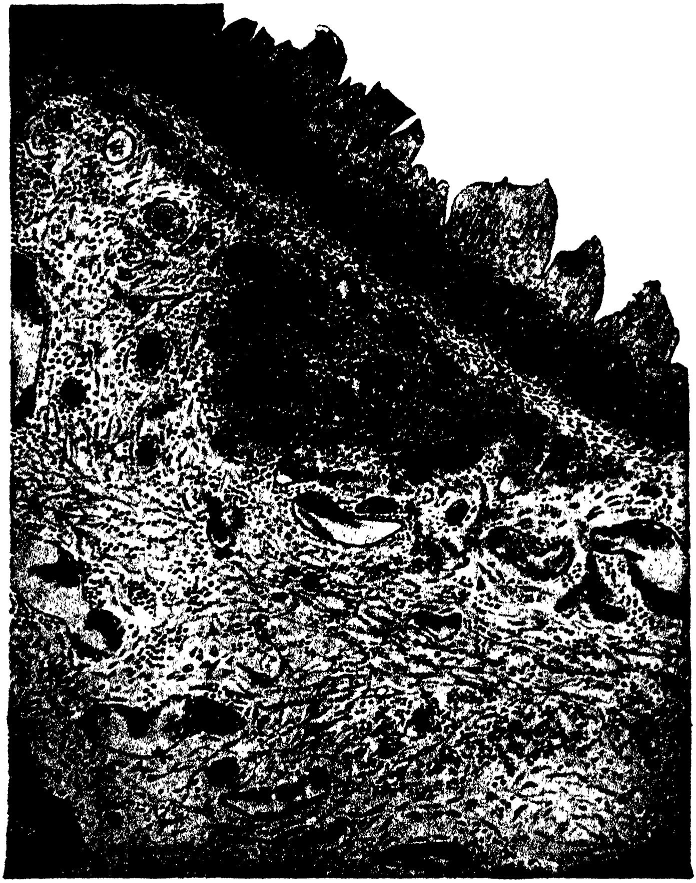


Fig. 66.—Microscopical section of large intestine in bacillary dysentery, showing necrosis of mucosa, cellular infiltration, and hæmorrhages into submucosa.

On clinical grounds, bacillary dysentery may be classified as follows :

1. *Mild or catarrhal bacillary dysentery.*—A common history is that for some days the patient had suffered from what was supposed to be an attack of diarrhœa. The stools, at first bilious and watery, perhaps four or five in the twenty-four hours, had latterly and by degrees become less copious and more frequent, less fæculent and more mucoid, their passage attended by a certain amount of straining and griping.

At the same time the tongue may remain clean, and there may be no accompanying pyrexia. The attack may be over in a week, and the stools may not number more than twelve in the twenty-four hours. The majority of these mild cases are due to Flexner, Schmitz or Sonne bacilli.

2. *Acute bacillary dysentery.*—In others the onset is much more abrupt. Within a few hours dysentery may be in full swing. The stools, at first fæculent, soon consist of little save blood-stained mucus. Very shortly the desire to stool becomes increased, the griping and tenesmus being accompanied, perhaps, by distressing dysuria. Fever, which at the outset may have been smart and preceded by rigor, subsides. The face is anxious and pinched: the cheeks are high-coloured from a toxic flush. Slight delirium and mental confusion may be added to the clinical picture. Thirst may be considerable, anorexia complete, and the tongue white or yellow-coated. In a week or more the urgency of the symptoms may diminish, and the attack tapers off into a subacute or chronic condition, or it may end as abruptly as it began (Chart 22).

3. *Fulminating bacillary dysentery.*—These are invariably Shiga infections. The attack generally begins suddenly, it may be in the middle of the night, with chills or smart rigor, vomiting, headache, and a rapid rise of temperature to 100° or even 104° F. Very shortly after the rigor, purging begins, the stools rapidly assuming dysenteric characters. In from two to three days up to a week or longer, vascular failure sets in with a subnormal temperature, and the patient dies, or the toxæmia may be so virulent that death may take place before dysenteric stools are passed. The tongue is thickly coated, and other signs of an acute toxæmia are present. The abdomen is sunken and acutely tender. The stools rapidly become liquid, offensive, and greenish or greyish. Towards the end, neither blood nor mucus may be visible in the almost uncountable evacuations.

A *choleraic* form, in some respects resembling cholera, has been noted. The onset is acute, with vomiting. Collapse with its attendant phenomena sets in early. The stools are liquid, serous, light-coloured, with blood and mucus flecks. The temperature is subnormal and death may take place within three days.

4. *Relapsing bacillary dysentery.*—In a proportion of bacillary dysenteries, although the urgency of the initial attack may subside, dysenteric symptoms do not completely disappear. The stools may recover their fæculent

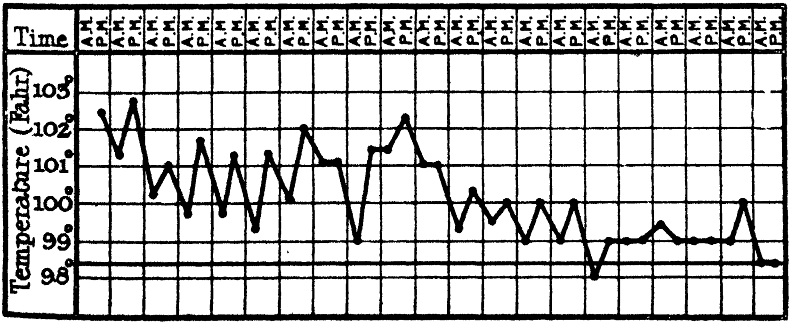


Chart 22.—Bacillary dysentery.

character, or may even show some signs of formation, yet they continue to be passed too frequently, often preceded by griping, and contain a variable amount of muco-pus, with or without blood. Cases of this type may be due either to a fresh, or to recrudescence of an old infection.

5. *Chronic bacillary dysentery.*—In quite a large proportion of cases of acute dysentery the fæces do not become absolutely normal for a considerable time after abatement of the more urgent symptoms. On the slightest indiscretion, the old symptoms re-appear, provoking unexpected attacks of diarrhœa. For months, or even years, some patients never pass a perfectly healthy stool, the unformed motion always containing muco-pus and at times blood. Often there is a tendency to scybalous stools, or to constipation alternating with diarrhœa.

Since the end of the 1914–1918 war a type of chronic bacillary dysentery has been quite common; it differs from any previously described. The initial attack may have been so mild that it has passed unnoticed, but recurrences take place, with passage of blood and mucus, becoming more frequent and intense as years go by. Eventually the stools resemble those of chronic ulcerative colitis.

The following varieties may be distinguished:—those with superficial ulceration from which the causative organism may be isolated by rectal swabs; those without actual ulceration, but with patches of granulation tissue in which cultures are negative; and finally those with generalized mucoidal inflammation and deep involvement of the bowel wall.

The course of these cases tends to be progressive, and, unless vigorously treated with sulphaguanidine they may terminate fatally. Emaciation may be extreme, especially in native races; an adult may weigh less than 49 lb. (Fletcher and Jepps.) Considerable anæmia may develop, with cardiac failure and dropsy. Death may ensue from exhaustion, or from some intercurrent disease, such as tuberculosis or malaria.

Bacillary dysentery in children.—Infection with dysentery bacilli (Shiga or Flexner) in small children, especially Europeans, may produce most acute and rapidly fatal symptoms. They may die in convulsions before the intestinal symptoms have had time to develop. The cases may resemble meningismus, and at the onset, on account of pyrexia and toxæmia, simulate enteric infections.

Post-dysenteric ascites.—Megaw is of the opinion that the ascites which is so common in most hospitals in India is a sequel to bacillary dysentery. When bacillary dysentery is not treated, or is improperly handled, the dysenteric toxins pass through the intestinal wall and set up an irritative peritonitis which is followed by fibrosis of the peritoneum. The result is ascites, which, according to Snapper, may be associated with liver cirrhosis. Massive serous intraperitoneal effusions, which may prove fatal, have been recorded from the Middle East.

Symptoms of Sonne dysentery.—In most cases mild attacks of dysenteriform diarrhœa are the rule. The fæces are greenish, or yellowish and offensive, with blood-flecked mucus from which the organism may be cultured. In the more acute attacks the symptoms more closely resemble those of Flexner dysentery, with sudden onset of colic, diarrhœa and, later, blood and mucus. Sometimes, however, they are still more acute, with pyrexia and vomiting, and may assume an alarming aspect reminiscent of salmonella infections. Then "tomato soup" stools are passed, followed by rapid prostration. Sonne infections are usually pyrexial at the time of the abrupt onset, but in the milder cases the fever is slight and transient. A feature is associated catarrh of the respiratory tract with diarrhœa. Rhinitis may precede the abdominal symptoms. Acute Sonne infections in children up to nine years of age may cause sudden death. Some observers believe that in this instance the symptoms are produced, not so much by the organisms, as by their toxins in contaminated food, which forms a favourable medium for their propagation. In mental institutions especially Sonne infections are apt to attack the inmates.

Cruickshank and Swyer found that, by repeated examination of fæcal specimens and rectal swabs, Sonne's bacillus could be isolated in most cases, and that the latter method gave a higher proportion of positive results. The Sonne bacillus persists in the intestine in a gradually decreasing proportion of cases after subsidence of the acute manifestations. Thus, the convalescent carrier becomes an important reservoir for its spread. Three consecutive negative laboratory reports should be obtained before the patient is released from hospital.

Predisposing causes.—Bacillary dysentery is especially apt to attack those who are in an enfeebled state owing to starvation, unsuitable dietary, physical exhaustion or exposure, or whose health has been undermined and resistance lowered by some chronic disease such as malaria, tuberculosis, scurvy or enteric. In the feeble-minded, in very young children, in the aged, and in pregnant women, bacillary dysentery is apt to assume a serious toxic aspect. Young children usually show pronounced symptoms of toxæmia, and die in convulsions or in coma.

Complications.—*Dysenteric arthritis*, or *dysenteric rheumatism*, has long been recognized in India. Effusions into the cavity and ligaments surrounding the joints, especially the knee and ankle, may take place during the acute stage, or, more generally, during convalescence when the stools are fæculent (Fig. 67). It may be common in some Shiga epidemics, absent in others. Considerable pyrexia is usually present. The condition may last a considerable time, but usually clears up without leaving deformity, though, exceptionally, permanent disability may result. According to Graham, complete recovery eventually ensues, even after arthritis has persisted for six months. Aspirated synovial fluid is sterile,[1] but agglutinates dysentery bacilli (Klein) in a titre considerably higher than that given by blood-serum. This condition has to be distinguished from fugitive serum-arthritis, such as sometimes occurs after injection of anti-dysenteric serum, and also from acute rheumatoid arthritis.

Eye complications.—Acute *conjunctivitis* and *iridocyclitis* are now regarded as symptomatic of dysenteric toxæmia. The former is frequently seen in association with arthritis, whilst iritis supervenes in a small percentage of cases. The pupils are irregular in outline, with ring synechiæ. There is also anterior uveitis, with adhesions to the capsule of the lens, formed by a thin exudate occupying the pupillary space, causing photophobia, blepharospasm and marked circumcorneal hyperæmia. The aqueous humour has been found to agglutinate Shiga's bacillus, though the tears do not contain specific agglutinins. That the eye and joint complications are due to the dysenteric toxin is indicated by experimental work on animals. This shows that the filtrates of Shiga cultures, when injected intravenously, produce iritis and arthritis, as well as local lesions in the cæcum.

---

[1] Shiga's bacillus has been isolated from the fluid in one instance (Elworthy).

Other complications.—Parotitis, unilateral or bilateral, has been often observed. Intussusception of the small intestine has been found in children, and in acute cases may cause death.

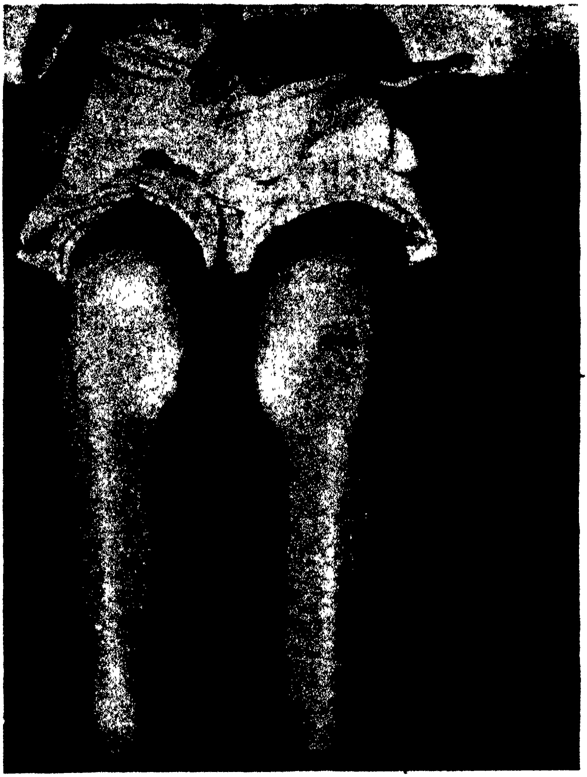


Fig. 67.—Arthritis of hands and knees in bacillary dysentery.

During the present war in the Middle East the list of complications has been amplified to include intestinal hæmorrhage, perforation with peritonitis, chronic peritonitis with localized or general effusion of peritoneal fluid, pneumoperitoneum, portal pyæmia with multiple liver abscesses, thrombosed piles, rectal prolapse, peripheral circulatory failure in toxic cases, renal failure in Shiga infections, pneumonia, and diffuse purpuric rashes. Non-specific urethritis is now also recognised.

Renal failure which has clinical resemblances to that found in traumatic anuria (crush injury) results from various factors, in which dehydration and toxæmia play a part, leading to reduced glomerular filtration and degenerative changes in the tubules. The urine contains granular casts and albumin, so that azotæmia and oliguria ensue, and may end in uræmia.

Sequelæ.—Stenosis of the large intestine may result from an acute attack. Pain and abdominal discomfort may indicate abdominal adhesions which are an occasional sequel. Rarely, megacolon may, apparently, be produced. Mucous colitis frequently persists for years. *Peripheral neuritis* of the legs may follow bacillary dysentery. *Post-dysenteric tachycardia*, or effort syndrome, a condition of irritable heart, may persist long after dysenteric symptoms have disappeared. *Achlorhydria*, rarely *achylia gastrica*, may be responsible for digestive troubles which may follow dysenteric infections.

Bacterium coli infections of the genito-urinary tract frequently complicate chronic bacillary dysentery as the result of the specific kidney lesions produced by dysenteric toxins. This possibly is the explanation of the comparative frequency of this infection in tropical residents.

Bacillary-dysentery carriers.—The " carrier question " in bacillary dysentery is probably not so serious as in typhoid, as the bacilli remain confined to the intestines and to the mesenteric glands.

There are many circumstances which render the " carrier state " in bacillary dysentery difficult to detect. Dysentery bacilli, as a rule, are scarce and likely to escape detection in a fæcal stool, though with improved methods of isolation by desoxycholate agar, the carrier rate has been found to be about 10 per cent. It is probable that carriers are the starting-point of an epidemic. The majority are " *convalescent carriers*," a term which implies that the patients have incompletely recovered, and continue to pass blood and mucus and dysentery bacilli in their stools. There is no evidence that the gall-bladder acts as a reservoir, as in typhoid; or that the " carrier state " persists for any great length of time. The organisms continue to live in mucous retention cysts in the intestinal mucosa, in collections of pus from beneath the scars of ulcers or beneath their edges. The maximum period that this carrier state can last is about three years.

Carriers of Flexner bacilli are much commoner than those of Shiga. Generally, the Flexner carrier is in good health, while the Shiga carrier is more or less an invalid.

Sometimes bacillary inflammation or ulceration is localized to the lower rectum (granular rectitis). These patients pass blood and mucus in their stools, though otherwise in good health. The bacillus may be isolated, by means of rectal swabs, a year or more after the initial attack. Fortunately they are easily cured by sulphaguanidine (*see* p. 482).

Microscopic examination of the fæces usually affords little assistance in these cases. The chances of isolating the specific bacillus are considerably increased by making cultures direct from the mucosa by rectal swabs, or from scrapings of ulcers obtained through the sigmoidoscope.

Dysentery bacteriophage.—D'Herelle observed that filtrates of convalescent dysentery stools developed the property of clearing broth cultures of Shiga's bacillus, but when a few drops of filtrate were added to a fresh culture, the bacilli were again dissolved, and that this process could be repeated indefinitely. Shiga's bacillus was first recognized as susceptible to bacteriophagy. The bacteriophage consists of ultra-microscopic particles measuring 20–30 $m\mu$. Many races of bacteriophage are virulent for Shiga's bacillus, but that obtained from Flexner bacilli is active solely for the homologous organisms. Bacteriophage has been isolated from the stools of patients convalescent from acute and mild bacillary dysentery. It appears probable that improvement in the clinical condition coincides with the increased bacteriophagic potency. Dysentery bacteriophages have been prepared for therapeutic use.

Diagnosis.—Difficulty in the diagnosis of bacillary dysentery on clinical grounds is mainly confined to the milder forms. Whenever possible, a confirmatory laboratory diagnosis should be carried out.

The possibility of malaria in the course of bacillary dysentery should always be borne in mind. The concurrence of a subtertian malaria with bacillary dysentery may be particularly serious.

A tentative diagnosis may be made from a microscopic examination of the *cellular exudate* in the stools by the method known as cyto-diagnosis. For this purpose the specimen should be procured fresh from the patient and as early as is possible in the disease. The characteristic feature of the bacillary stool (Plate XI), is the preponderance of swollen *polymorphonuclear leucocytes*, with distinctive ring-like nuclei, which constitute over 90 per cent. of the total cell elements in the stool. The examination should be conducted with a $\frac{1}{6}$-in. lens and a low ocular (× 2).

Macrophage cells (*histiocytes*).—These cells, sometimes 20–30 μ in diameter, are derived from the endothelium of the capillary vessels. They may be round, oval, or even bilobed. They are hyaline, and contain in their substance vacuoles, fatty granules, ingested red blood-corpuscles, or even, occasionally, leucocytes. They are non-motile, but, owing to their phagocytic activities, are apt to be mistaken for *Entamœba histolytica.*

The differential-cell picture in dysenteric exudates has been distinguished by Alexeieff as a " pyogram." In amœbic dysentery fæces the cellular elements are few and mononucleated ; in bacillary dysentery, numerous and polymorphonuclear, with *pseudopyknotic nuclei.*

It is important that the significance of macrophage cells in bacillary dysentery stools should be emphasized. Willingness to diagnose amœbic dysentery is very pronounced in almost every tropical country. It is most important that pathologists should acquaint themselves with the appearance of inflammatory cells in the fæces, as well as with the different stages of the dysentery amœba, before an expert diagnosis is given. The main features of the cyto-diagnosis of dysentery stools were pointed out by the Editor in 1912 and this method was practised throughout the 1914–1918 war, since when, especially in recent epidemics, its value has been amply confirmed.

Entamœba coli and flagellate protozoa (*Chilomastix* and *Trichomonas*) may be seen in considerable numbers in a bacillary-dysentery exudate, especially during the convalescent stages. Some difficulty may be experienced in differentiating *E. coli* from *E. histolytica* in bacillary-dysentery stools.

Isolation of the dysentery bacillus.—The stool should be collected in a bed-pan, *which should contain no disinfectant*, and the patient should be warned against passing urine. A portion of freshly-passed blood and mucus should be picked out by a platinum loop, and, if soiled with fæces or urine, should be rinsed in 5 c.c. of distilled water or normal saline solution. The earlier in the illness, the easier it is to isolate the dysentery bacillus. It is, as a general rule, difficult when the dysentery has lasted five days or longer. Fæces despatched for laboratory examination through the post, or by messenger over long distances, should be emulsified with a double volume of buffered glycerol saline—1 part of glycerine to 2 parts of saline, buffered by the addition of 5 per cent. acid sodi phosph., at *p*H8. The mixture is tinted with phenol red so that any change in acidity can be detected. Dysentery bacilli are very delicate, and never occur in great numbers, even in a freshly-passed stool. The mucus, or two loopfuls of the suspension, should be spread, in a spiral manner, somewhat thickly, upon a MacConkey agar plate, or, better, on desoxycholate citrate agar, which inhibits to some extent the growth of *Bact. coli*. The plate should be incubated at 37° C. in an inverted position for eighteen hours, when the small blue transparent colonies can be examined with a watchmaker's lens. As a rule, Shiga colonies are more refractile and of a more regular outline than are those of the Flexner-Y group. It is a good plan to hold a piece of dark paper against the back of the plate to make their recognition easier.

Identification of the colonies may be carried out as follows: four or more should be picked off with a platinum spud and transplanted on to agar slopes, and, after further incubation, these subcultures should be emulsified and tested in high dilutions against Shiga and Flexner sera in agglutination tubes. The macroscopic method is usually employed, or the test may be performed on a microscope slide or on the agglutinometer. By means of a capillary pipette, drops of bacillary emulsion are placed together with an equal quantity of specific sera diluted to 1 in 50. The resulting dilution will then be 1 in 100. After oscillation for three minutes, should the reaction be positive, snowflake agglutination occurs.

After these measures, diagnosis may be confirmed by inoculating subcultures of the organism into the sugars (Table VII, p. 468). Direct culture by the rectal swab method offers obvious advantages and results in a higher proportion of positives.

Isolation of the dysentery bacillus post mortem.—The bacillus can be isolated from the acutely inflamed mucosa by washing the canal free from intestinal contents and scraping off the blood and mucus with a platinum loop, but from necrotic mucosa this is by no means easy. In this case the surface must be first seared with a hot knife or glass and incised, and material for culture obtained with a platinum loop from the bottom of the incision.

Serological diagnosis.—This is of little value as an aid in the early stages of the disease, or in the very acute or rapidly fatal types in which it is so important to arrive at an accurate diagnosis. The sera of some patients, proved to be suffering from bacillary dysentery by isolation of the specific organisms from the stools, may give negative agglutination reactions.

For the diagnosis of Shiga infections in convalescent or chronic cases, positive agglutination of over 1 in 25 should be obtained. In Flexner infections an agglutination of 1 in 100 indicates positive diagnosis. Davies found dysenteric agglutinins were present in dysenteric stools, even when absent from the serum of the patient, especially during the first week. Blood and mucus from the fresh exudate are shaken up with normal saline, filtered and put up for agglutination in the same way as serum.

Serological diagnosis may be of considerable assistance in chronic bacillary dysentery, where high-titre agglutinations are sometimes obtained, especially with emulsions of the pooled Boyd strains of Flexner bacilli.

Serological diagnosis of Sonne dysentery by the agglutination test is also somewhat unreliable, and appears to depend, to some extent, on the strain of organism employed as antigen.

An intracutaneous test for Shiga dysentery, with Shiga toxin, was introduced by Brokman (1923). A negative reaction is diagnostic of infection. Dreyfuss (1944) used a Flexner vaccine (5 million bacilli), which gives a cutaneous reaction in positive cases.

Sigmoidoscope examination.—Sigmoidoscopy reveals pathological changes in the colon and therefore plays an important part in the differential diagnosis of the dysenteries. It is especially useful in chronic cases, and should be employed wherever practicable. For preparation of the patient, a cathartic of ½ oz. of castor oil is given : the following morning the bowel is cleared out by a warm-water enema. If the patient has acute diarrhœa, omission of castor oil is advisable, though in any case it should not be given later than 2 p.m. on the day preceding examination. It is advisable to give 10–15 min. of tincture of opium half an hour before in order to render the rectum less sensitive. The mucous membrane of the rectum is replaced by granulation tissue with surrounding hyperæmia, and has a characteristic appearance resembling the cortex of a granular kidney ; at the same time infiltration of the bowel can be detected (Plate XIII). Superficial oval or circular ulcers, up to 1 cm. in diameter, are also seen in the chronic stage, and sometimes even pseudopolyposis of granulation tissue. In the healing stage the mucous membrane is rose-pink and slightly nodular. Widespread superficial pitting at the site of former ulceration is characteristic and it is possible by this feature to state definitely that the patient had suffered from bacillary dysentery. The passage of the instrument is attended by pain due to stretching of the bowel wall. This is almost diagnostic, as in amœbic ulceration it is usually painless.

Differential diagnosis of the dysenteries will be dealt with on p. 525.

Prognosis depends very much upon individual susceptibility and physical condition. In the jails of India, in fact throughout that country, though bacillary dysentery is widespread, the case-mortality is very small. In many thousands of cases among British troops in the 1914–18 war, it is doubtful whether it at any period rose above 5 per cent. Epidemics in native races have been recorded where the mortality was over 28 per cent., and others among debilitated Solomon Islanders in which it was 47 per cent. Prognosis is unfavourable in chronic cases, especially in poverty-stricken, malaria-infected, half-starved natives.

Treatment.—The patient should be placed in bed on the appearance of the first signs, and should on no account be permitted to get up in order to pass his motions. A bed-pan should therefore be employed wherever nursing facilities are available. In the choleraic or fulminating cases in which the passage of stools is incessant, and the physical exhaustion consequently very great, it may be advisable to dispense with a bed-pan altogether. The patient should then be placed upon a waterproof sheet with a gamgee dysentery pad. For this purpose the attendant, for self-protection, should wear rubber gloves, as the discharges are highly infectious.

The stools should be periodically inspected, for by these, supplemented

Fig. 1. Acute bacillary dysentery (Shiga infection). Note œdema of mucosa and submucosal hæmorrhages.

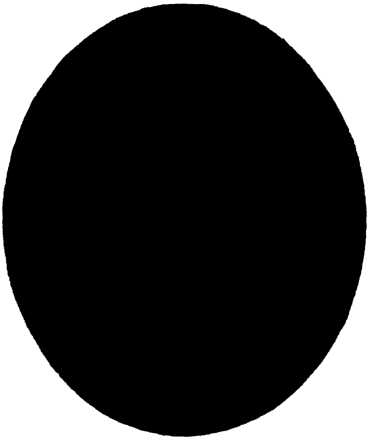


Fig. 2. —Chronic bacillary dysentery (Flexner infection). Note granulations on mucous membrane.

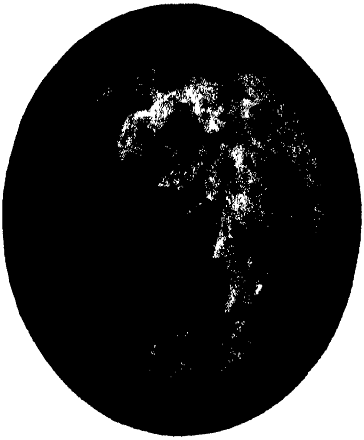


Fig. 3. Acute amœbic dysentery. Note folding of lax mucous membrane, pin-point ulcers and surrounding submucous hæmorrhages.

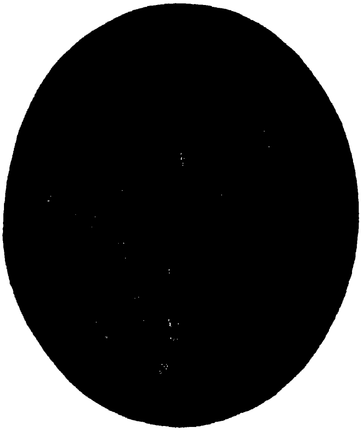


Fig. 4. —Chronic amœbic dysentery. Note diamond-shaped ulcers and submucous hæmorrhages.

SIGMOIDOSCOPIC APPEARANCES OF RECTUM IN BACILLARY AND AMŒBIC DYSENTERIES.

PLATE XIII

TABLE VIII

Diagnosis between Bacillary and Amœbic Dysentery

BACILLARY DYSENTERIES	AMŒBIC DYSENTERY
Acute diseases with a tendency to epidemic spread. "Lying down dysentery."	A chronic endemic disease. "Walking dysentery."
Incubation period short, 7 days	Incubation period long, at least 20–90 days ; it may be more.
Onset acute.	Onset insidious.
Pyrexia common.	Pyrexia rare, unless complicated.
Course days or weeks.	Course usually prolonged for years.
Complications : Polyarthritis frequent ; eye complications.	*Complications :* Hepatitis, abscess of liver ; abscesses more rarely in other situations. Pericolic abscess. Amœbic infection of skin.
Death due to— (*a*) Exhaustion. (*b*) Toxæmia. (*c*) Glomerulonephritis.	Death due to— (*a*) Exhaustion. (*b*) Perforation. (*c*) Hæmorrhage. (*d*) Liver abscess.
Signs : Tenderness over whole abdomen, more marked over sigmoid flexure.	*Signs :* Local tenderness and thickening, mostly over sigmoid flexure, transverse colon, and cæcum.
Tenesmus very severe.	Tenesmus not usually noted.
Pathology : Acute diffuse necrosis of mucous membrane of large intestine, due to dysenteric toxins.	*Pathology :* Local lesions confined solely to the large intestine, due to the characteristic ulcers.
Ulcers : When present, on free edge of transverse folds of mucous membrane and distributed transversely to long axis of gut.	*Ulcers :* Commence as small abscesses of submucosa in long axis of gut. "Flask-shaped ulcer," or *Bouton en chemise*, "sea anemone" ulcers.
Serpiginous in outline, with ragged undermined edges, often communicating with neighbouring ulcers ; bases consist of granulation tissue.	Oval, regular, flask-shape in section, involving all coats ; bases consist of necrotic black tenacious sloughs ("Dyak-hair" sloughs).
Intervening mucous membrane hyperæmic. Ulcers rarely perforate. No compensatory thickening of bowel-wall.	Not uncommonly perforate ; compensatory thickening of bowel-wall. Intervening mucous membrane normal.
Stools : Scanty ; many in number. Bright blood-red, gelatinous, viscid mucus, odourless, resembling red-currant jelly.	*Stools :* Fæces intermingled with blood and mucus, resembling anchovy sauce (sago-grain stool). Offensive, smelling of decomposing blood ; generally copious.
Reaction : Alkaline.	*Reaction :* Acid.
Microscopic picture : Numerous red cells ; polymorphonuclears numerous, with clear-cut ring nuclei, Macrophage cells. Few micro-organisms visible (Plate XI).	*Microscopic picture :* Red cells numerous and in clumps, polymorphonuclears damaged, often extruded nuclei. Macrophage cells scanty. Large numbers of motile bacilli and ***Entamœba histolytica***, generally with ingested red cells. Charcot-Leyden crystals common (Plate XII).
Blood examination : Leucocytosis in the early stages.	***Blood examination :*** Usually a moderate leucocytosis throughout.

by the appearance of the tongue and the general condition of the patient, the progress of the case can best be ascertained.

Attention should be paid to the diet, which should be nutritious and easily assimilable, leaving as little residue as possible. Nothing but water should be given for the first twenty-four hours. The best diet is one consisting of tea, jellies, albumin water, rice water, chicken soup, beef tea, Brand's essence, arrowroot, Horlick's, Bengers, sago puddings, any of which may be given at two-hourly intervals in small quantities (6–10 oz.), slightly warmed, at each feed. Non-residue diet should be instituted when blood and mucus have disappeared from the stools. Treatment should be preceded by a mild purge, the most suitable being sodium or magnesium sulphate. The routine treatment with saline aperients was once almost universally employed, but is not now recommended, especially in dehydrated cases.

Sulphaguanidine (p-amino-N-guanylbenzene sulphonamide) is a guanidine analogue of sulphapyridine. It was first prepared by Buttle and colleagues, though Marshall and others described its chemical constitution. It exerts a bacteriostatic effect on various bacteria *in vivo* and *vitro*. It is moderately soluble in water, insoluble in strong alkali.

High concentration can be obtained in the intestine associated with low concentration in the blood (2–5 mgm. per 100 c.c.) and tissues. Urinary excretion is three times as rapid as that of other sulphonamides. Although sulphaguanidine may be excreted as crystals, no renal complications have so far been reported. The drug is undoubtedly less toxic than other sulphonamides. The toxic reactions observed include headache, malaise, purpuric skin rashes, mild pyrexia and anæmia. Agranulocytosis or jaundice have never been observed.

The dosage of sulphaguanidine in acute bacillary dysentery is: an initial dose of 0·1 grm. per kilo (or 9½ gr. to the stone (14 lbs.) body weight), a maintenance dose of 0·05 grm. per kilo four-hourly for the period during which the number of stools exceeds five per day, and a further maintenance dose of 0·05 grm. per kilo every eight hours until the stools have been normal in number and consistency for two days. Duration of treatment should not exceed fourteen days. If necessary, the course may be repeated. In chronic bacillary dysentery larger doses are necessary: 0·1 grm. per kilo every eight hours for the first five days, followed by a dosage of 0·05 grm. every eight hours for another five days; this may be repeated in fourteen days. The total dosage in acute cases varies from 18 to 350 grm.; the average effective dose in acute cases is about 130 grm., sometimes between 100 and 200 grm. In less acute cases the dose should be 18 grm. in the first twenty-four hours, administered in 6 grm. doses three times daily and subsequently 3 grm. three times daily for five days.

The effects may be judged by the change in the patient's general condition and the improvement in the stools which, in most cases, become porridgy and fæcal in forty-eight hours. A diminution in temperature, pain and toxæmia take place within twenty-four hours. The mortality rate, in the very extensive series so far reported upon from the Middle East is less than 1 per cent. Succinyl sulphathiazole (sulphasuccidine) appears to be equally effective, according to Poth and colleagues, especially for children. Sulphapyridine and sulphamethazine in maximal doses are also curative, but are more depressing and much more toxic. According to Fairley and Boyd, sulphaguanidine treatment should be combined with preliminary dosage with magnesium and sodium sulphate and, after two hours, with gentle colonic lavage with one pint of normal saline.

The indications for sulphaguanidine treatment are : cases of proven Shiga dysentery, or other infections with dysentery bacilli with frequent dysenteric stools, toxæmia and dehydration ; cases with collapse, profuse vomiting and choleraic stools ; all cases over 40 years of age, and those who develop acute bacillary dysentery in the course of some other illness. Very large doses of sulphasuccidine can be given with safety, and it is apparently even more effective than sulphaguanidine.

Opium.—Either by the injection of morphia or in solution, opium is indicated as a means of promoting sleep and relieving pain, if very severe.

Bolus alba (*kaolin*).—As a means of checking the diarrhœa and of eliminating the dysentery toxins in the intestinal canal, a mixture of animal charcoal and kaolin has been utilized in Germany and in Austria ; the powder should be given suspended in water in doses of three teaspoonsful every few hours. Crooke's collosol kaolin has much the same effect.

Anti-dysenteric serum.—Since the introduction of sulphaguanidine the value of antidysenteric serum has been discounted. It is now employed principally in toxic Shiga cases. Refined anti-Shiga serum, prepared by the Pope process of partial peptonization containing 20,000 International Units per c.c., is given intravenously in doses of 5 to 10 c.c. and may be repeated daily. The anti-toxic effects appear to be transient. It is best combined with sulphaguanidine therapy. No serum reactions have been observed with this new preparation.

Bacteriophage treatment.—Recovery from an acute attack of bacillary dysentery is connected with production of a corresponding amount of bacteriophage in the intestinal canal. A potent anti-Shiga phage has been prepared by d'Herelle, Morison, and others, but it is particularly difficult to obtain accurate statistics on the efficacy of this treatment. This phage is distributed in ampoules in quantities of 2 c.c. The patient takes three ampoules by the mouth daily, or it may also be injected *per rectum*. Whenever this method has been subjected to critical analysis, as in the Middle East during the present war, the results have not been conclusive, although it appears to have acquired a reputation in Egypt.

Relief of pain.—During the early stages of an attack the patient may suffer much from griping and tenesmus. These are generally relieved by a hot bath, hot fomentations, or turpentine stupes, three or four of which may be sewn into a piece of flannel and laid on the abdomen. This application has the advantage of being very light, of not wetting the clothes, and of keeping warm for many hours. Tenesmus and dysuria are best relieved by hypodermic morphia ; by an enema of a wineglassful of thin starch containing 40 or 50 drops of tincture of opium ; or by suppositories of morphia and cocaine. Washing out the lower bowel with a pint of hot water, with or without boric acid, is sometimes effectual in removing for a time, or, at all events, mitigating, the incessant desire to go to stool and to strain. Bismuth carbonate, 2 dr., with tincture of opium, 30 min., and thin starch, 2 oz., is also a good sedative enema. Painful colic or peristaltic action may be counteracted by the following mixture :

℞	Tinct. belladonnæ	♏vii	(0·414 c.c.)
	Pot. brom.	gr.x.	(0·648 grm.)
	Tinct. chlor. et morph. co.	♏x	(0·592 c.c.)
	Syrup. aurant.	ʒi	(3·55 c.c.)
	Aq. menth. pip. ad	℥ss	(14·2 c.c.)

Ft. mist. ℥ss t.d.s., p.c., vel p.r.n.

Collapse from dehydration and vascular failure may occur at almost any stage. An attempt should be made to restore the balance by the intravenous injection of large quantities of saline and glucose. Blood and plasma transfusions have been employed in these cases with striking benefit during the present war.

Vomiting and hiccough in severe cases should both be regarded as serious.

Treatment of complications.—*Arthritis* is best treated by application of Scott's dressing, radiant heat, or sand-baths at 45°–60° C.

Sulphaguanidine treatment appears to be specially efficacious.

When the joint is greatly distended the excessive fluid may be aspirated. *Iritis* is treated by atropine, the use of an eye-shade and the usual measures.

The treatment of chronic bacillary dysentery has been radically altered since the introduction of sulphaguanidine, which should be given in full doses over a prolonged period of fourteen days or longer. Fairley and Boyd, by periodic sigmoidoscopic examination, observed healing of chronic ulcers, and even those with exuberant granulations and pseudopolyposis appear to do well, but it is often necessary to repeat the course of sulphaguanidine. In refractory cases it may be necessary to inject the sulphonamide by retention enemata, in doses of 7–10 grm. daily, suspended in water and mucilage (7–10 ounces). This medicated enema is retained from three to four hours.

Moro's apple dietary has been used extensively in chronic dysentery in Germany, both for adults and children ; twenty or more apples made into a purée are eaten daily. A preserved apple powder, *Aplona*,[1] is made in Switzerland. In grave cases nothing besides Aplona is given for three days. The dose for adults is 1–1½ oz. (3½ oz. of Aplona = 360 calories), and the amount required for a day is divided into portions, each of which must be freshly prepared with boiled water at drinking temperature, or with weak tea, 60–120 gr. to ¼ pint of liquid. It must not be brought to boiling point and no sugar should be added, but saccharine may be substituted. After the third day it may be added to gruel or milk, being first mixed as a smooth paste with water.

Surgical treatment of chronic bacillary dysentery.—When less heroic methods fail, and the patient's condition is slowly but progressively deteriorating, right inguinal colostomy offers a reasonable chance of success. More usually, *appendicostomy* is performed. The cæcum and colon may now be washed out with normal saline, or with an astringent solution, such as tannic acid (2 per cent. solution), through the appendix, as frequently as desired. For this purpose a No. 8 rubber catheter with a copper stylet, and rectal tube with an outflow tube are used. The patient should lie on his back ; but should the cæcum get distended and the fluid fail to pass freely, turning on the left side will restore the flow.

---

[1] Sold by Coates and Cooper, 94 Clerkenwell Road, London, E.C.1.

Cæcostomy and ileostomy.—In cases with pseudopolyposis of the mucous membrane and incessant distressing blood-stained diarrhœa, the operation of valvular cæcostomy should certainly be given a trial. The results have been successful in some cases which were incurable by other means. A Paul's tube is first inserted into the cæcum and the fæces are allowed to escape through it, thereby placing the whole of the large intestine at rest. Then an efficient opening is made. The lower bowel may be washed out daily with boric acid solution, and the opening may be closed at some subsequent period, after the large bowel has been permitted to rest for three months or more ; complete recovery of the mucous membrane has been observed by sigmoidoscopic examination. A colostomy bag is fitted. The patient may be sent to convalesce and encouraged to consume plenty of fresh eggs, milk and fruit. One-barrelled ileostomy is sometimes preferable and is recommended by some surgeons. The indications here are the same as in ulcerative colitis, but it condemns the patient to a permanent colostomy belt and other disagreeable sequelæ.

Ispaghula.—The boat-shaped seeds of *Plantago ovata* have acquired a popular reputation in the treatment of chronic dysentery in India. The seeds are either chewed, when a gelatinous substance exudes which acts as a demulcent, or the pericarp is made into a paste. If taken in 1-dr. doses three times daily, it has a soothing effect. Singh recommends a fresh decoction prepared daily by boiling two drachms of the seeds in one pint of water, and subsequently straining. Chopra has shown that these seeds contain a glucoside *aucubin.* The mucilage which exudes from the seeds is acted upon by the digestive enzymes and coats the inflamed mucosa.

Prophylaxis.—The prophylaxis of bacillary dysentery consists principally in securing a pure water supply and in avoiding unwholesome and contaminated food ; also in eliminating flies from latrines and in protecting food against them. In barracks, camps, lunatic asylums, and other public institutions, bacillary dysentery should be regarded as an infectious and readily communicable disease, and therefore patients suffering from mild symptoms, or even looseness of the bowels, should be isolated.

To prevent the spread of bacillary dysentery in closely crowded communities, it is important to recognize, as early as possible, all carriers and mild cases which might otherwise escape recognition. Cunningham and others have pointed out that, in the prevention of the spread of bacillary dysentery in jails, it is essential that the stools of the inmates should be inspected daily. Any inmate found passing blood and mucus, even in small quantities, should be regarded as potentially infectious and as possibly constituting a carrier of the disease.

The treatment of carriers.—The chronic carrier has in the past been difficult to treat effectively, but sulphaguanidine has transformed the situation. It is recommended that this drug should be given in maximal doses for periods of 5–7 days, though it is usually necessary to repeat the course. For the drug to exert its maximum action, the fæces must be kept as fluid as possible by means of sodium or magnesium sulphate. Carriers of Sonne's bacillus appear to be especially difficult to cure.

Prophylactic inoculations.—The Japanese workers, and later Gibson in England, introduced an inoculation by which the toxic effects of the bacillus are neutralized by a potent anti-Shiga serum, resulting in an almost complete absence of reaction. The vaccine and serum (sero-vaccine) are enclosed in twin phials, the bacillary emulsion being contained in one arm, the serum in the other. The first dose was 0·25 c.c., containing 500 million Shiga organisms mixed with 0·1 c.c. of serum; the second dose, given 10 days later, contained 1,000 million organisms with 0·2 c.c. of serum. The results were distinctly in favour of this method of protection.

A similar preparation was used in Germany and in Austria as "*Boehncke's Dysbakta.*" Besredka produced an antidysenteric bilivaccine consisting of dead dysentery bacilli with the addition of bile. The technique is to give on three successive days before breakfast a dose of bile, followed by a pill containing the desiccated vaccine.

Blanc and Caminopetros employed intramuscular injections of *living vaccines* consisting of 4–6 thousand million dysentery bacilli, and found that they caused slight reactions which resolved three or four days later. They concluded that there is no particular danger in using living vaccines.

Trials are being made with preparations containing dysenteric endo- and exotoxins, and also phenol-extracts of the O antigen of *B. Shigæ*; this latter excites the appearance of specific agglutinins in the serum after inoculation (Morgan and Schutze).

II. AMŒBIC DYSENTERY AND AMŒBIASIS

Definition.—Amœbiasis denotes infection with the protozoon, *Entamœba histolytica.* When confined to the intestinal canal it produces *amœbic dysentery,* or primary intestinal amœbiasis. This is insidious in its onset, chronic in its course, and with a marked tendency to relapse. When metatastic lesions are produced in the liver and elsewhere it should be known as secondary, or *hepatic amœbiasis.*

Geographical distribution.—Amœbiasis occurs to a greater or lesser degree throughout the tropics and subtropics. During recent years sporadic indigenous cases have been found in Northern Europe (Russia, Norway and Germany) and even, rarely, in Great Britain. Specially prevalent in India, Indo-China, China, and the Philippines, it is common throughout North and Central Africa, widespread in the Southern United States, South America, and the West Indies.

Epidemiology and endemiology.—A disease of insanitation, not necessarily requiring tropical or subtropical conditions for its propagation, amœbiasis arises sporadically without seasonal prevalence, but does not usually occur in epidemic form in the same manner as the bacillary dysenteries. Wenyon and O'Connor have shown that the cysts of *E. histolytica* can be demonstrated in the fæces of house-flies sixteen hours after ingestion, and that flies play a part in the dissemination of amœbiasis. There is also much evidence that *contaminated water* and even fresh vegetables, such as lettuce, may constitute sources of infection.

Reports of the outbreak in Chicago in the summer and autumn of 1933 gave the total number of cases as 1,409, in that city or traced to other cities in the United States, with over 40 deaths. The source was traced to two hotels, where the majority of those infected were servants or guests. All carriers of *E. histolytica* were removed from employment, but in spite of these measures, cases continued to develop amongst employees of one hotel, where the " carrier " rate was found to be as high as 47·4 per cent. Further investigations revealed serious contamination of the water supply from defective drainage and that drinking water formed the main channel of infection.

Considering the susceptibility of the cysts to desiccation, it is probable that dust and sand play no part in dissemination.

Intestinal amœbiasis is a disease of adult life as a rule. It is rare in European children under five years of age, but among Egyptians of the poorer class in Cairo, Perry and Bensted found that 13 per cent. of clinical dysentery was due to *E. histolytica.* Biggam diagnosed acute amœbic dysentery with liver abscess in an infant three months old, and Williams found it in a negro infant of fifteen months on the Gold Coast. As the disease has a long incubation period and is acquired from contaminated water and vegetables, it is unlikely to occur among carefully nurtured children, in whom the bacillary form is much more common.

Intestinal amœbiasis may produce active symptoms for many years. The Editor has treated infections which have persisted from thirty to forty years without seriously undermining the patient's health, so tolerant are the tissues to *E. histolytica.* There appears also to be a difference in incidence of intestinal amœbiasis in the sexes. Males, European and native, are more apt to contract the infection. Gharpure and Saldanha (1930) reported that in a series of over 400 post-mortem examinations the number of male cases was quite disproportional to the total. Of amœbic dysentery and liver abscess, 90·3 and 93·8 per cent. respectively occurred in males ; 9·4 and 6·2 per cent. in females. Below ten years of age the incidence of amœbic lesions was 0·9 per cent. and of liver abscess nil. The highest peak is reached in the decennial periods 20–40, with a proportion of about 30 per cent. of amœbic dysentery and 38 per cent. of liver abscess to the total number of autopsies.

In Armenia, Zaturjan showed that amœbiasis in children usually runs a much more benign course than in adults and rarely shows any serious complications.

Ætiology.—The discovery of amœbæ in dysentery stools was made by Lösch in 1875. Originally regarded as a single organism—*Amœba coli*—it is now recognized, mainly as a result of the work of Schaudinn, Hartmann, Wenyon, and Dobell, that several distinct species occur in the intestinal canal of man, one of which, *Entamœba histolytica*, is pathogenic for man, while others—*Entamœba coli, Endolimax nana, Iodamœba bütschlii* and *Dientamœba fragilis*—are harmless species. *E. histolytica* was originally cultured on egg-medium by Boeck and Drbohlav in 1925 (p. 1018), but during the last few years it has been grown on a variety of serum-media. The term *Entamœba* is employed by English authorities, though American writers claim that *Endamœba* is more correct.

Detection of Entamœba histolytica in stools.—When present in stools, entamœbæ are generally easy to find. It is necessary to pick out a small fragment of stool shortly after it is passed, and to lay it on the slide and compress it under the cover-glass to form a fairly transparent film. Active entamœbæ tend to occur in clumps or masses and are not evenly distributed throughout the stool; they may be present in one evacuation but not in the next. Care should be taken that the receptacle in which the stool is collected is free from all traces of antiseptic. These amœbæ live in the fæces for a few hours after being passed and are readily distorted in the presence of urine. The dysentery amœba is a clear, faintly greenish-tinted, transparent body, as a general rule, some three to five times the diameter of a red blood-corpuscle. In its vegetative or tissue-invading phase it is recognizable by its active movements, as well as by the presence of extraneous material, such as red blood-corpuscles, which it ingests. The nucleus may sometimes be excentric. The habit of ingesting red blood-corpuscles and body-tissue cells is one of the points of distinction between *E. histolytica* and non-pathogenic *E. coli*.

In fresh and in stained preparations[1] the amœba is seen to be made up of two zones—a granular endoplasm surrounded by a clear protoplasmic ectoplasm. The nucleus shows a characteristic uniform structure if the specimen is fresh and fixed while alive; aberrant forms with fragmented karyosomes, etc., are due to degenerative changes (*see* p. 865).

These amœbæ flow, rather than move, across the slide, and in the living state do not always exhibit conspicuous differentiation between ectoplasm and endoplasm. They quickly die and degenerate outside the body. At lower temperatures they remain stationary, but when the slide is warmed, they eject from time to time hyaline "blade-like" pseudopodia (Fig. 68). Degenerating entamœbæ often contain vacuoles, but these are not normally present. When conditions become adverse, they encyst, first passing through a precystic stage.

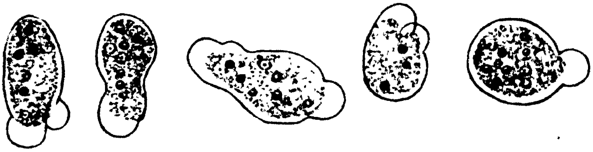


Fig. 68. Camera lucida drawings showing protrusion of pseudopodia by *Entamœba histolytica*. (*P.H.M.-B. del*)

Cysts.—Cysts vary much in size. They contain highly refractile masses of chromatin or chromatoid bodies, which may assume the form of blocks with rounded ends, and also glycogen-containing vacuoles. When first formed, the cyst contains one nucleus, which measures about one-third of its diameter. This divides by binary fission, so that finally, in the more mature individuals, four small nuclei, each measuring one-sixth of the diameter of the cyst, are produced. In general characters the nucleus of the cyst resembles that of the vegetative stage.

Cysts of *E. histolytica* can survive outside the body of man for about ten days if kept moist and cool. Desiccation kills them immediately, though they survive much longer at lower than at higher temperatures.

Westphal has recorded a significant experiment where an apparently harmless *E. histolytica* infection was acquired by the ingestion of cysts. Some months later cultures of bacteria isolated from the fæces of acute amœbic dysentery were ingested and a similar dose was given to a control. Both the "carrier" of *E. histolytica* and the control suffered from diarrhœa, but on the twenty-third day, the former developed clinical amœbic dysentery. It was finally determined that super infection with Flexner bacilli excited the clinical manifestations of amœbic dysentery. Some workers therefore believe that symbiotic bacilli aid, or in some way instigate attacks of acute amœbic dysentery.

---

[1] For the staining of amœbæ in liquid preparations, *see* Schaudinn's method (Appendix, p. 1012). The details of amœbæ are distorted if attempts are made to dry the specimen as in a blood-film.

Summary of life-history of Entamœba histolytica.—The active vegetative entamœbæ live on the tissues of the gut-wall, where they ingest blood-corpuscles and multiply by mitosis. In primary amœbic lesions they make their way into the follicles of the large intestine, where they multiply and, partly by pressure, partly by cytolysins, dissolve the interglandular tissues, producing small amœbic abscesses in the submucosa which burst and become ulcers. A number of amœbæ enter the lumen of the bowel, encyst, and pass out with the fæces. The precystic individuals, which are free from protoplasmic inclusions, congregate on the surface of the bowel. They are smaller than the vegetative forms which continue to multiply in the tissues. Typical cysts, smaller than precystic forms, are quadrinucleate when fully mature. When swallowed by another host they pass into the small intestine, where they hatch into amœbulæ which attack and invade the tissues. (*See* Appendix, p. 866).

This summary epitomizes the generally accepted account of the life-history of *E. histolytica*, but there are some observers, notably Reichenow, who consider that it is normally an inhabitant of the lumen of the intestinal tract and not a tissue-invader, but that, under certain conditions, the amœbæ may invade the intestinal wall and thereby give rise to clinical amœbic dysentery. He thinks that the normal form is the *minuta* form, which lives in the intestinal lumen, where it reproduces by binary fission and produces four-nucleated cysts. Westphal, on the other hand, regards *E. histolytica* as capable of both intra- and extra-cellular digestion. Proteolytic ferments, not toxins, are produced. Colonization is in the tissues.

A characteristic feature of amœbic infection of the intestine is the periodic variation in intensity, which may be connected with resistance on the part of the tissues of the host, or possibly constitutes a feature in the developmental cycle of the parasite.

Occasionally, however, vegetative amœbæ migrate from their site in the bowel-wall and, as tissue-invading forms, enter the venous system and are transported to the liver, exceptionally to the spleen, brain or lung; but by so doing they become unable to complete the cycle of development as observed in the intestine, for pre-cystic individuals and cysts never develop in these situations. Amœbic infection of the skin has been seen quite often (*see* p. 521).

E. histolytica passers.[1]—The healthy passer (or excretor) of *E. histolytica* is an individual who has not suffered, and is not suffering, from dysenteric symptoms, but passes *histolytica* cysts, though otherwise in good health. Such cyst-passers may have active entamœbæ in the tissues of the bowel.

The cyst-passers may be divided into two classes—(1) *contacts* who have never suffered from clinical amœbic dysentery, and (2) *convalescents* who have recovered from an attack. It is known that, for every abnormal person who is suffering from amœbic dysentery with passage of vegetative forms which are non-infective to other individuals, there are large numbers of healthy persons who continue to pass *E. histolytica* cysts, thus constituting a perennial source of infection. The vegetative entamœba must, in either case, exist on the tissues of the host. We know from post-mortem findings in the Philippines, New Orleans and elsewhere that ulceration can occur without producing signs or symptoms, and it is well known that liver abscess may be produced under these circumstances.

---

[1] "Cyst-passer" is here used in the place of "carrier," a term which is not applicable to *E. histolytica*

In Faust's opinion the conception of amœbic invasion of the human bowel should include milder types of tissue damage. In a series of accidental deaths in New Orleans thirteen cases of *E. histolytica* infections were disclosed, of which seven showed amœbic lesions. There were three types:—(1) initial pinpoint ulceration, (2) shallow crater-like lesions, (3) extensive very shallow denudation of the mucosa. None of these destructive processes extended beneath the muscularis mucosæ.

The lesions of the mucosa may actually be microscopic. Cytolysis and necrosis of the epithelium is followed in the majority of instances by rapid regeneration, so that probably only a small percentage develop clinical evidences of amœbic dysentery. The experiments of Walker and Sellards showed that out of 20 men fed with *E. histolytica* 18 became parasitized, but only 4 developed dysenteric symptoms, though the remainder continued to pass cysts in their stools.

By intrarectal and intracæcal injection of fæces containing cysts into cats and puppies, ulceration of the bowel-wall and hepatic abscesses have been produced; but, although the fæces may be swarming with active vegetative forms, no cyst-formation has ever been observed in these animals. Similar lesions have been produced in kittens by intrarectal injection of cultures of *E. histolytica.*

Infection in carriers of *E. histolytica* is remarkably persistent and, in all probability, unless cured by anti-amœbic treatment, these persons continue to pass cysts for the remainder of their lives.

Craig and other American authorities believe that everyone who harbours *E. histolytica* cysts is a candidate for some more serious complication and that therefore every "carrier" should receive adequate treatment.

Incidence of cyst-passers or carriers.—Among British soldiers after a year's service in Egypt, Wenyon and O'Connor found that there was no marked difference between carriers who had previously suffered from dysentery and those who had not (the percentages being 6·5 as against 4·5 per cent.). The carrier rate among native Egyptians, as might be surmised, was considerably higher, 13·5 per cent. The most surprising outcome of the systematic examination of fæces by protozoologists during the 1914–1918 war was the almost universal presence of the histolytica carrier. Yorke, Matthews and Malins Smith found a considerable percentage of carriers among lunatics, army recruits, and the personnel of the navy in England. The two former recorded 5 per cent., the latter 19 per cent.; Kuenen found a considerable number of indigenous infections in Holland, and Brug estimated the carrier-rate as 12·7 per cent. in that country. In the United States amongst schoolchildren it may be as high as 10·8 per cent., but in adults Andrews and Paulson gave a much lower figure, 0·2 per cent. In New York City it is 1·1 per cent. among city dwellers, and 5·4 per cent. among foodhandlers, and in Philadelphia 5·2 per cent. for the general population. Craig has estimated that 10 per cent. of the total inhabitants of the United States are infected with amœbiasis. The exact significance of these figures is difficult to determine. It certainly does not mean that this comparatively large number is suffering from gross ulceration of the bowel, for indigenous *amœbic dysentery* is almost unknown in England. Even among the insane, with a relatively high cyst-passer rate, "clinical amœbic dysentery" is rare.

Pathology.—The earliest lesions of amœbic dysentery are minute yellow hemispherical elevations of the mucosa, which mark the site of a deeper-lying zone of necrosis. By growth in size and localized necrosis they form flask-shaped ulcers, the bases of which lie in the submucosa. These ulcers are scattered throughout the large intestine, rarely extending above the ileo-cæcal valve. The appendix may be involved, and Musgrave, in 1910, reported three cases of fatal peritonitis due to this; since then a few other cases have been investigated in which entamœbæ were demonstrated in microscopic sections. Amœbic ulceration of the ileum was described by Biggam. These were acute and rapidly fatal cases, and in neither instance were amœbæ demonstrated in the stools but only in preparations from the lesions. Active amœbæ and cysts were found in the duodenal juice in one patient in Germany.

The ulcers may not be larger than a pin's head or may measure an inch or more in diameter, and, as the disease progresses, may become even larger. Then the margins are rolled, the edges undermined, and the base is formed by fibres of the muscular coat (sea-anemone ulcers). The ulcers are capped by dense yellow, green, or even black sloughs (Dyak-hair sloughs), which may project into the lumen of the bowel. The lesions usually originate in the cæcum, and are scattered throughout the transverse and sigmoid colon and rectal canal, though the intervening mucous membrane remains healthy. Amœbic lesions commonly extend throughout the large intestine as far down as the internal anal sphincter.

In 186 cases examined *post mortem* by Clark in 1924, lesions were scattered throughout the colon in 61 per cent. affecting, in order of frequency, cæcum, ascending colon, iliac colon, sigmoid, rectum and hepatic flexure. At the sites where intestinal stasis is greatest there is a tendency for amœbæ to invade the bowel wall.

In chronic amœbiasis there is inflammation and compensatory hypertrophy of the bowel-wall. Sometimes sacculation and constriction of the large intestine may be produced by cicatrization (Plate X, Fig. 1).

Sellards and Leiva demonstrated in experimental animals that when the cæcum is exposed and infective material is introduced into the lumen, infection takes place with surprising regularity, but that, whether it is introduced directly into the cæcum or *via* the rectum, initial lesions occur in the extreme lower part of the bowel. Stasis in the large intestine affords the organisms a foothold, and is a factor in determining the location of the initial lesion. Wagner and Beiling, whose conclusions are almost identical, found that the amœbæ at these focal points enter the tissues in one of three ways, passing directly into connective tissue, crypts, or lymph-channels, where they migrate to the lymph-follicles and the submucosa. The intestinal mucosa responds to invasion by secreting mucus, which, when mingled with blood, forms an excellent medium for the development of amœbæ on the bowel surface. The balance between host and parasite is delicate.

Thrombosis of the blood-vessels, in which entamœbæ are often found, occurs at the bases of the ulcers, and, by erosion, an arteriole may be opened, and rarely severe or fatal hæmorrhage result. Perforation by ulcers, even massive gangrene, especially of the cæcum, may occur, and lead to fatal peritonitis.

In the healing gut, cicatricial pigmented scars mark the sites of former ulcers. Adhesions may form between proximal coils of intestine which become matted together or adherent to the liver and spleen. Pericolic abscesses may sometimes form.

In chronic cases, polypoid or gangrenous tags project into the lumen of the gut. The intestinal contents may be composed of dark, almost black hæmorrhagic fæcal matter with characteristic penetrating odour.

Carcinoma may originate at the site of healed amœbic lesions.

The cadaver shows no signs of toxic absorption, such as occurs in the bacillary dysenteries. Apart from wasting, the other viscera exhibit few, if any, changes.

Histology.—The amœbæ work their way down the crypts of Lieberkühn, multiply, and, by secretion of cytolysins, disintegrate the tissues of the submucosa and produce gelatinous necrosis, with a little surrounding tissue reaction and round cell infitration (Fig. 69). In more advanced lesions the entamœbæ may be seen between the muscular fibres and within the peritoneal veins, whence they may be swept as emboli into the portal vein, lodge in the liver, and so become the starting-point of an amœbic hepatitis or liver abscess.

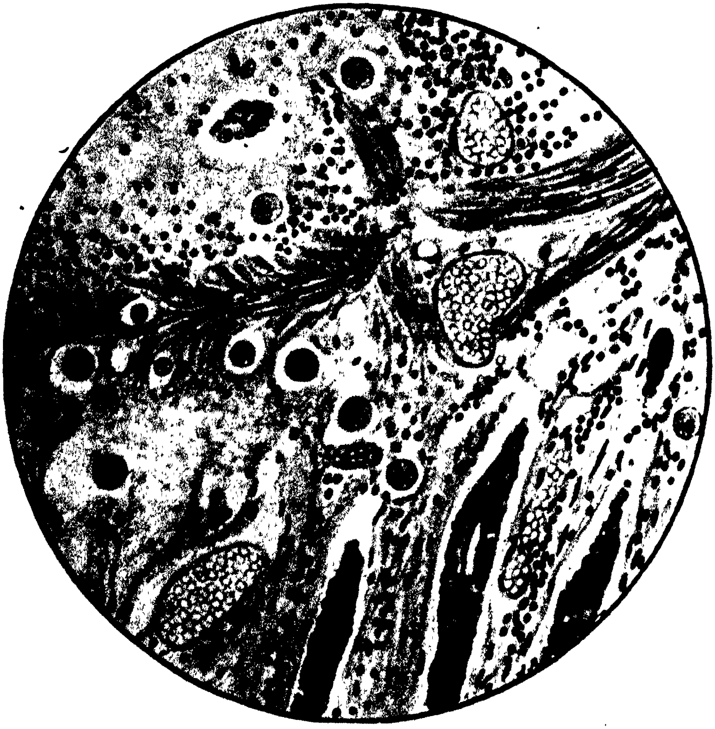


Fig. 69.—Section through base of amœbic ulcer, showing *E. histolytica* in the tissues. (*C. M. Wenyon*)

The superficial layers of the slough of an amœbic ulcer become secondarily invaded by bacteria, though the adjacent mucous membrane remains healthy and shows few microscopic changes. The precystic forms of *E. histolytica* are found in the intestinal mucus and on the surface of the bowel.

Experimentally-produced amœbic dysentery in kittens differs essentially from the disease seen in man. When introduced into the rectum of the cat, entamœbæ produce, within two to three days, acute inflammation. The lesions differ in their generalized and acute character from those observed in man. Death takes place from secondary terminal bacterial invasion. Cysts are never found, and chronic ulceration does not occur.

Symptoms.—The *incubation period* of amœbic dysentery, from the time of introduction of the cysts into the intestinal canal until the development of symptoms, is of considerable length. In the Chicago outbreak of 1933 it ranged from seven up to seventy-seven days, symptoms appearing occasionally within one week though, in a few instances, not for three or four months. The fact that amœbic cysts are found in the fæces of individuals who may never have had " dysentery " in the ordinary accepted sense, suggests that the development of clinical symptoms depends upon some secondary bacterial infection.

The great majority of cases of amœbic dysentery run a chronic course, with frequent intermissions and relapses. This latency is one of the most striking and characteristic features of amœbic dysentery. The *onset* is generally insidious, so that the patient may complain more of diarrhœa than of dysenteric symptoms. Perforation of the bowel, leading to fatal peritonitis, has been known to occur in patients who, judged by clinical data, were not suffering from dysentery. In mild cases the patient generally complains of suddenly developed *amœbic diarrhœa.*

The symptoms, subjective and objective, may resemble those of bacillary dysentery ; but, as a rule, abdominal tenderness is much less acute, and may be restricted to the cæcum, where it may simulate appendicitis, or to the transverse colon, where it may mimic gastric ulcer ; more frequently it is limited to the sigmoid flexure. Should ulceration occur in the rectum, tenesmus and straining may be noted. The individual stools are larger than those of bacillary dysentery. They may not exceed three or four in the twenty-four hours, and are seldom more than twelve. As a rule, they contain much dark and altered blood, which imparts a penetrating, disagreeable odour. In consistence and appearance they resemble *anchovy sauce.* Often, blood-streaked mucus is intermingled with liquid fæces. Melæna may occur occasionally. The motions may be formed, and streaked with blood and mucus. Gangrenous sloughs may be voided. Unless the case is complicated by hepatitis, when the liver is painful and enlarged, there are seldom any toxic manifestations. *Acute* cases of amœbic dysentery with high fever and urgent painful and severe clinical manifestations are rare. In the Chicago epidemic acute cases of unusual severity, with pyrexia and other toxic manifestations (amœbic fever), were noted.

The patient, as a rule, becomes emaciated, but some remain in remarkably good condition, although suffering from repeated relapses. The Editor has seen patients, suffering from chronic amœbic dysentery, become grossly fat. Sometimes the skin is myxenoid and the complexion has a subicteric tinge. The tongue is moist and coated. Vomiting may rarely occur. Generally there is a complete anorexia. Dysuria is not noted as in bacillary dysentery, and *tenesmus* is rare. The *liver* is sometimes enlarged, even in the absence of hepatitis.

In uncomplicated amœbic dysentery there is no pyrexia, but cases with periodic rigors, suggestive of malaria, are occasionally met and may be recognized by amenability to emetine treatment and by discovery of amœbic cysts in the fæces. In amœbic dysentery there is usually a moderate leucocytosis (10,000–12,000 with low proportion of polymorphonuclears—about 70 per cent.).

There still remain a number of obscure conditions of which some mention must be made. It is probably true, so variable are the symptoms of amœbiasis, that almost any intestinal disease may be simulated. Intestinal amœbiasis is *not invariably associated with dysentery or diarrhœa.* It may occasionally be marked by constipation, by intestinal pains or disturbances, very often by neurasthenia, bodily and mental lassitude, furred tongue, and disordered digestion, popularly described as an "uncomfortable belly," or "growling abdomen." In these cases discovery of amœbic cysts in the fæces, followed by appropriate treatment, may improve the clinical condition. Pathological changes in the bowel may sometimes lead to sacculation or even dilatation of the colon. Very often the cæcum is grossly distended with gas and the source of much discomfort. In chronic cases, infiltration of the sigmoid colon, less commonly of the cæcum, can be detected by abdominal palpation.

In the course of chronic amœbiasis cachexia ensues, resembling intestinal toxæmia. These patients have muddy complexions resembling in outward appearances some cases of diverticulosis.

Often, without treatment, symptoms may subside, and the patient may be apparently cured, but will relapse after an interval of weeks, months, or even seven years or longer. More often he continues to pass loose, semi-formed stools. Attacks of diarrhœa alternate with constipation. After any physical exhaustion, chill, alcoholic or dietetic indiscretion, a fresh exacerbation may supervene. On account of these variable symptoms, the infinite variety of abdominal pain, and the occasional melænic stools, it is clear that amœbic dysentery has to be differentiated from duodenal ulcer, gall-bladder disease, pancreatitis and neoplasm.

Hepatitis.—Acute amœbic hepatitis may supervene at any time during the course of amœbic infection, while the symptoms are acute, or during a remission. The patient usually experiences great pain over the hepatic area[1], together with signs of toxæmia and considerable pyrexia. The liver itself is enlarged; it may project below the costal margin to the level of the iliac crests, and be extremely tender. Pain referred to the right shoulder is also frequent. Usually there is a leucocytosis of twenty to thirty thousand with low proportion of polymorphonuclears.

Hepatitis may subside without any active treatment. There is some evidence that in these cases the amœbæ are distributed throughout the liver, with embolic spread, suggesting a portal distribution. Fortunately it is particularly amenable to emetine treatment (*see* p. 517.)

: he inclines to the right and tries to protect his liver. He carries it in his hands, so to speak.

Complications.—Death may result from exhaustion, intestinal hæmorrhage, perforation, or liver abscess.

The most frequent complication of amœbic dysentery is liver abscess.

Perforation of the bowel may be sudden, or be preceded by intense local pain, which, when restricted to the right iliac fossa, may be mistaken for appendicitis. Occasionally, pericolic abscess may be produced, especially in the descending or sigmoid colon. Intestinal obstruction from an amœbic granuloma (amœboma) has been recorded, and when this forms in the cæcum it may resemble hypertrophic tuberculosis or malignant disease.

Amœbiasis may be superimposed upon bacillary dysentery, or *vice versa*. In Egypt, intestinal amœbiasis is often found associated with *Bilharzia mansoni*. Visceroptosis, distension or sacculation of the gut, leading to intestinal stasis, may constitute distressing results of amœbic dysentery, but stricture of the rectum does not ensue. *Appendicitis* due to amœbic ulceration is not uncommon. Snapper has recorded a psoas abscess as the result of perforation of an amœbic ulcer of the cæcum.

Sequelæ.—Many sequelæ of intestinal amœbiasis have been described. often on insufficient evidence, and it is very difficult to prove direct association of different obscure clinical states with a past infection with *E. histolytica*. The Editor believes that certain intestinal conditions occur frequently as the aftermath of amœbiasis ; such are appendicitis (not necessarily caused by amœbic ulceration), mucous colitis, and *duodenal ulceration*. Chronic amœbiasis, besides producing chronic ill-health, very often contributes to introspection and neurasthenia.

Diagnosis.—It is safe to regard acutely developing tropical diarrhœa either as bacillary or amœbic dysentery, though clinical distinctions in the less acute manifestations are often unreliable. Assistance in diagnosis may be obtained from the more rapid onset, the febrile condition. and the rapid pulse in the bacillary disease. As a rule, the number of stools in bacillary dysentery is greater and their individual size less. The character of the stools should also be taken into account. Usually they contain more dark blood in amœbic dysentery. Occasionally, however, they may be tarry, suggesting duodenal ulceration.

Laboratory diagnosis should always be resorted to, having regard to the experience of the observer and his ability to determine whether any amœba-like body discovered in the fæces is in fact *E. histolytica*, *E. coli*, or some large tissue cell, such as a macrophage (Plate XI). With practice this becomes comparatively easy. Entamœbæ may be absent in some portions of a stool, numerous in others. Several preparations must be searched, at first with the ⅔-in. lens, subsequently with the ⅙-in. Whenever possible, a portion of blood-stained mucus must be picked out for examination. The organisms may be difficult, or almost impossible, to detect in a specimen containing too much blood. It is important that the specimen should be as fresh as possible. The discovery of an active amœba containing ingested red blood-corpuscles is generally sufficient to establish the diagnosis of *E. histolytica*. In the more chronic and latent forms of the disease the characteristic cysts must be sought. Entamœbæ and their cysts can at first be recognized under a low-power lens as " bright stars," of higher refractility than other cells, especially with the eosin contrast method whereby the background is stained pink whilst cysts stand out as clear refractile objects. Examination should not be considered as completely excluding an amœbic infection until the stool has been searched on *each of seven* consecutive days. Cultural methods may assist diagnosis in scanty infections.

In cases in which there is any doubt of the identity of the cysts,[1] they may be stained by the rapid, or by the more prolonged iron-hæmatoxylin method (p. 1012). Mixing the fresh fæces with a solution of Weigert's iodine (p. 1012) brings out nuclei and other characteristics.

Charcot-Leyden crystals are commonly found in the fæces in amœbic dysentery, and their presence has been regarded as of diagnostic importance. The crystals vary very much in size, averaging 5–25 μ; their typical shape resembles a whetstone, and they are soluble in warm water, strong mineral acids, and alcohol. They may also be found in preparations from amœbic ulcers, made through the sigmoidoscope (Plate XII).

The Editor emphasizes the danger of attaching too much importance to Charcot-Leyden crystals as necessarily diagnostic of intestinal amœbiasis. He has found them in malignant disease of the rectum, mucous colitis, coccidiosis (*Isospora hominis*), ulcerative colitis, and various helminthic infections (*see* p. 1011).

Complement-fixation reaction (Craig).—Craig described a technique for the preparation of amœbic antigen and for carrying out this test, which is practically the same as that used for the Wassermann reaction. The antigen is an alcoholic extract of cultures of *E. histolytica* grown upon a modified Boeck-Drbohlav medium. A rich culture is selected and from this at least 120 sub-cultures are made. Then all the material at the junction of the egg slant with Locke's serum solution is pipetted into suitable tubes, centrifuged and the sediment extracted in the incubator at 37° C. for fifteen days with seven and a half volumes of absolute alcohol. Craig has now published results from 1,000 cases in which diagnosis was checked by the fæces examination. Of those giving a positive reaction (175), *E. histolytica* or cysts were found in the fæces of 89·7 per cent.

Meleney and Frye have tested the value of complement-fixation in experimentally infected animals inoculated parenterally with amœbic extracts. Experimentally infected dogs and monkeys usually gave a positive reaction.

Intradermal test.—The intradermal test of Scalas is as follows: the test material is obtained by mixing mucus containing *E. histolytica* with 30 c.c. of physiological saline solution, and incubating the result for one week at 37° C. with daily shakings and decolorization with animal charcoal. In positive reactions an indurated swelling at the site of inoculation is produced.

Sigmoidoscopic examination.—Amœbic ulceration may extend into the rectal canal, so that sigmoidoscopic examination, conducted without an anæsthetic, usually affords valuable information. Quite commonly, small yellow ulcers with surrounding hyperæmia are seen, especially in the region of Houston's valves. It is often possible to find living entamœbæ in the scrapings, even when they cannot be demonstrated in the fæces[2]. In contrast to chronic bacillary dysentery, instrumentation is practically painless. Amœbic ulcerations may be touched or scraped without causing any painful sensation. The mucous membrane surrounding individual lesions shows absence of inflammation, preserving its normal pink colour, but it is usually more reticulated and folded than normal,

[1] Concentration may also be employed for recognition of *E. histolytica* cysts (p. 1012).

[2] By this method the Editor has diagnosed amœbiasis in a case resembling enteric fever.

Amœbic lesions are then seen in the crypts between the folds, either as small, yellow elevations the size of a pin's head, or as superficial snail-track ulcers with hæmorrhagic margins (Plate XIII). Often the only signs of abnormality are small, flame-shaped hæmorrhages, in the centre of which the entamœbæ may be demonstrated in scrapings obtained by means of a long-handled Volkmann's spoon passed through the sigmoidoscope (Fig. 70). A porcupine quill forms a convenient instrument for transferring material from the spoon to the microscope slide.

In the Editor's series of 535 cases of intestinal amœbiasis, 509 were diagnosed by microscopic examination of fæces, in the remainder by demonstration of amœbæ in scrapings from amœbic ulcers. Out of 258 sigmoidoscopic examinations, characteristic amœbic lesions were demonstrated in 234.

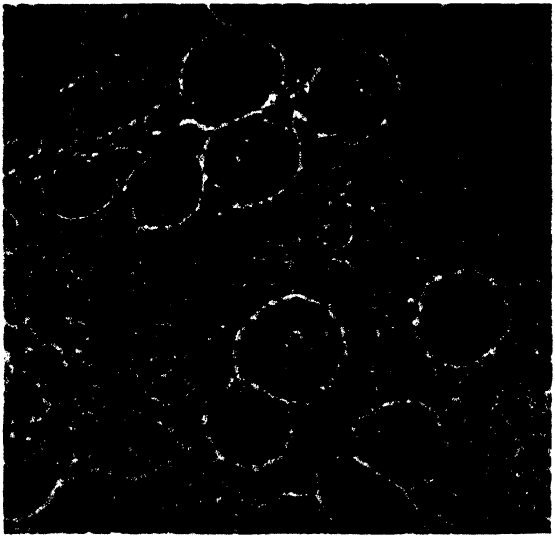


Fig. 70.—Amœbic dysentery, showing tissue-invading *E. histolytica* in scrapings of ulcer obtained through the sigmoidoscope.

In chronic, partially-healed amœbic dysentery, or even in symptomless cyst-passers, amœbic lesions may be distinguished as minute oval circular pits, or depressions, irregularly disposed. They may be almost microscopic, requiring a magnifying eye-piece for their detection. Occasionally solitary amœbic ulcers, resembling carcinoma, are seen in the rectum, twenty years or more after the primary infection. Fungating granulomatous masses (amœboma or amœbic granulomata) may be discovered.

X-rays in diagnosis.—Vallerino described, as indicative of amœbic lesions, filling defects in cæcum and ascending colon with deficient haustration of the bowel, seen after a barium meal, but not so easily after an opaque enema. X-ray diagnosis has been tried on an extended scale at the Hospital for Tropical Diseases, London. Occasionally filling defects have been observed in the cæcum, but similar appearances are seen in other forms of dysentery and colitis. Only unsatisfactory assistance can be obtained by this method.

Differential Diagnosis.—Differential diagnosis has to be made from many other conditions in which blood and mucus are passed in the stools, and this means differential diagnosis from all other forms of dysentery, colitis, or even other forms of intestinal disease. Differential diagnosis from malignant disease of the bowel deserves emphasis. Many observers—James, Willmore, Gunn, Howard, Haran and Mendelson—have described a hypertrophic form of intestinal amœbiasis—amœbic granuloma—which may affect different portions of the large bowel, cæcum, or sigmoid, and which may produce tumours 12 by 10 cm. in extent, and on account of these physical characters may resemble carcinoma and cause partial occlusion. The process consists primarily of an isolated ulcer, with progressive erosion of the bowel-wall in response to long-continued secondary infection. Gelatinous granulation tissue appears, and the process may affect the bowel-wall and neighbouring mesoocolic fat with enlargement of the mesenteric glands. Satisfactory diagnosis can usually be made by microscopic examinations of scrapings or by removing tissues by biopsy when entamœbæ may be demonstrated in sections. This also applies to the solitary ulcers described on p. 491.

Treatment

Many diverse drugs have been advocated for amœbic dysentery. Treatment requires careful supervision. Specific drugs may be preceded by a purge ; castor oil is the most appropriate. Opium, as a routine measure, should be avoided. The dietary should be carefully regulated and, in the acute stages, nursing is important. As all drugs used in the treatment of amœbiasis contain toxic principles, especially emetine and its derivatives, a definite diagnosis of amœbiasis must be made before they are exhibited. Unfortunately there is a reprehensible tendency to inject emetine indiscriminately as a diagnostic measure in all cases of dysentery.

Ipecacuanha.[1]—It had long been recognized in India and in the Far East that ipecacuanha root was a valuable drug in chronic dysentery ; this was Manson's opinion based upon a wide experience in China. Its use is now a matter of history, though it is sometimes employed and is still beneficial in the after-treatment of liver abscess or pulmonary amœbiasis (*see* p. 523). Food should be interdicted for three hours, and then 10 to 20 drops of laudanum given in a tablespoonful of water, and a mustard plaster applied to the epigastrium to counteract the emetic effects of the drug ; about twenty minutes later, when the patient is under the influence of the laudanum, 20 to 30, and even as much as 60 gr. of ipecacuanha, in pill, bolus, capsule, or suspension in half a wineglassful of water, are administered. The dose of ipecacuanha must be continued daily for at least a week.

I. Emetine.—There are four alkaloids of ipecacuanha—emetine, cephæline, psychotrine, and emetamine, but only the first-named has definite therapeutic properties. Emetine should be injected subcutaneously or intramuscularly. It is apparently a toxic drug, especially to children and women, when given *intravenously* or in excessive doses. It is a white crystalline powder, sensitive to light, soluble in four parts of water, and highly irritant to the eye.

Dobell showed that emetine is lethal to amœbæ in culture, a strength of one in five million. Nossina proved that this action is influenced by the acidity of the medium. It has a slight action in an acid medium, but the effect increases as the reaction approaches neutrality. The optimum is *p*H 6·8. Cephæline is far less effective. It is curious that emetine and cephæline, though pre-eminently active in preventing multiplication of *E. histolytica*, do not apparently exert any direct action. On the other hand, a derivative of emetine—dimethoxyemetine, which has a potent direct action, fails to cure the infection in man.

---

[1] Brasilian ipecacuanha root (*Cephaëlis ipecacuanha*) is said to be more efficacious than the preparation from New Grenada (*Uragoga granatensis*), as it contains more emetine.

In large doses, more than 1 grain a day, emetine is apt to produce toxic symptoms. It may lead to asthenia, cardiac irregularity, emaciation, mental depression, and in rare cases to myositis and even neuritis which may affect a particular group of muscles and produce partial paralysis. Thus, the Editor has seen atrophy of the scapulo-humeral group, resembling chronic poliomyelitis. In excessive doses it may actually produce diarrhœa. Emetine therapy is frequently followed by fine branny desquamation of the skin and an atrophic brittle condition of the nails. (Fig. 71.) Emetine injections exert no action on the pre-cystic forms of *E. histolytica*, and are therefore ineffective in chronic cases with cysts in the fæces.

Fig. 71.—Effect of emetine intoxication on the nails : increase of lunule, striation and brittleness. (*Dr. T. Jackson*).

Attention must be paid to the toxic manifestations of emetine when given injudiciously without proper indications. Being a cytoplasmic poison it is especially toxic when given to patients with bacillary dysentery. Apart from its general toxic action on the tissues, it has an especial affinity for the heart. This action has been shown by Epstein to be on the myocardium and the conducting fibres, and it may produce auricular fibrillation[1]. Improperly-conducted emetine injections, especially in debilitated persons, may produce fixation abscesses or widespread cellulitis, and the Editor has seen two cases where this was so extensive that the patient nearly lost his arm. Eczema, or even ulcers, may be provoked at the site of injection. Often the stiffness and irritation resulting from emetine injections are intolerable. Most of these drawbacks may be obviated by giving intramuscular injections. Emetine is specially toxic to young children and is mentally depressing to adults. It should not be injected intravenously.

---

[1] By electrocardiographic methods Heilig and others have shown that the cardiac effects have possibly

It should never be given hypodermically to patients who are leading an active life or taking hard physical exercise. This rule is too frequently disregarded, and permanent cardiac damage is the result.

It is best to initiate treatment with a course of deep subcutaneous or intramuscular injections of emetine hydrochloride (1 gr. in 1 c.c. of distilled water) daily for ten or twelve days. This does not suffice to eradicate the infection from the bowel, as the Editor has shown. It should therefore be supplemented by a course of the *double iodide of emetine and bismuth* (emetine-bismuth iodide). Emetine[1] injections are much more effective in *metastatic amœbic lesions* (hepatitis, etc.) than in intestinal amœbiasis.

The prevailing practice of giving periodic courses of emetine injections in chronic amœbiasis is subject to serious objections in so far as it tends to render *E. histolytica* emetine-fast and to make further treatment ineffectual. The renewed practice nowadays of giving heroic courses of emetine does not eradicate the infection but poisons the patients.

II. Emetine-bismuth iodide was introduced by Du Mez in 1915 and later it was popularized by Dale. It contains 58 per cent. of iodine and 28 per cent. of emetine. In the intestine the insoluble salts of bismuth are converted into bismuth sulphide after passing the pylorus. It is indicated especially in chronic cases and in persistent passers of *E. histolytica* cysts and is given by the mouth. More usually known as E.B.I., it is an insoluble powder, from which the emetine is set free by contact with the intestinal juices. It was formerly said not to be decomposed in acid solution (e.g. gastric juice), but this is incorrect. It passes through the intestinal canal unabsorbed, if compressed into a hard tablet, or if coated with some insoluble substance, such as paraffin, vaseline, resin, keratin, or stearin. It is best made up in powder form in gelatin capsules (*Slipules*), or mixed with jam or syrup. The maximum individual dose for an adult is 3 gr. (0·2 grm.) per diem for ten to twelve consecutive days. Experience has shown that individual doses of 2 gr. suffice and that a total dosage of 20 gr. will entirely eradicate infection. For delicate individuals and women the dose should begin at 1 gr. and be gradually increased. This drug is more easily tolerated in temperate climates than in the tropics.

The drug is dispensed as a red powder; the capsules of gelatin are manufactured as *Slipules*. No. 5 size capsule will contain 1 gr. of E.B.I. If the full dose is given, it is better from the point of view of the patient to take one capsule containing 2 gr., but when treatment is commenced with smaller doses the patient becomes gradually accustomed to the drug.

If gelatin capsules have been kept for some time, they tend to harden and become insoluble. They should therefore be pricked with a pin before being administered.

It is important to observe certain precautions in giving this drug. When given at 10 p.m., the last solid food should be taken at 6 p.m. The patient should remain at rest; he should endeavour to go to sleep, and any saliva should be wiped from the mouth.

---

[1] Disagreeable sequelæ of emetine injections may be avoided if the skin is pinched and the inserted *deep subcutaneously*.

Vomiting and diarrhœa are to be expected in the earlier part of the course, and are to be viewed as an indication that the drug is being absorbed. Diarrhœa is a necessary prerequisite to cure, because precystic forms of *E. histolytica* live on the mucous surface of the bowel where they are not affected by hypodermic emetine but are killed by the alkaloid in the lumen of the bowel[1]. If no symptoms of nausea supervene, it is probable that the cachets are not being dissolved and their contents freed. It is necessary for the patient to remain in bed and take a liquid or milk diet with eggs and toast.

Excessive vomiting and nausea may be mitigated by 10–15 min. of *tinct. opii* given half an hour previously, or, in some patients, by nepenthe, luminal, allonal, or chloretone. Most patients lose about 5 lb. in weight while under treatment. The condition of the heart and pulse should be noted daily, but treatment should not be discontinued unless depression becomes severe. Almost invariably a fall in blood-pressure (about 20 mm. of mercury) ensues. Alcohol in any form should be prohibited. When the cure is completed the patient should be gradually permitted to resume activity, though dieting (*see* p. 504) may still be necessary.

For relapsing cases it was formerly considered necessary to give more than one course of E.B.I. and some cases were thought to be due to amœbæ which had become resistant to emetine. Too much reliance should not be laid on isolated fæces examinations, on account of the vicarious appearances of cysts, but it is advisable to re-examine fæces microscopically at the end of six weeks. The results of treatment are much better controlled by periodic sigmoidoscopic examinations. For some considerable time after disappearance of active lesions, small pits or depressions of the mucous membrane may be seen.

A modification of E.B.I.—emetine periodide (E.P.I.)—is less toxic. It may be given in capsules in dosage of 3 gr. daily, in conjunction with capsules of dried ox-bile, gr. 5, which facilitates liberation of emetine. The Editor prefers E.P.I. for those who cannot tolerate E.B.I.

Auremetine (Willmore and Martindale) is a combination of emetine with auramine (a dye). It is given by the mouth as a dark-maroon powder which is insoluble in water. It is less easily decomposed than E.B.I. in the gastric juice. The dose, 1 gr. in gelatin capsules (slipules), is given four times daily on alternate days for seven days, and then daily until a total of 40–60 gr. has been taken.

III. Iodine-oxyquinoline-sulphonic-acid preparations (*Quinoxyl*) —Sodium-iodoxy-quinoline sulphate is also known as *Chiniofon* (B.P.), *Yatren* (Bayer), *Quiniosulphan* (May & Baker), *Anayodin* (U.S.A.)[2] and *Dysentulin* (German). It is a mixture of four parts of 7-iodo-8-hydroxy-quinoline-5-sulphonic acid, containing not less than 26·5 per cent. combined iodine, and one part of sodium bicarbonate. There is some chemical reaction, so that the preparation may contain a small amount of sodium hydroxyquinoline sulphonate, in addition to sodium bicarbonate and iodohydroxy-quinoline sulphonic acid. In solution 100 parts of quinoxyl yield approximately 85 parts of iodohydroxyquinoline sulphonate. Quinoxyl can be given either by the mouth or by retention enema. By the former route the maximum daily dose is 1 grm. (15 gr.) in powder form, in capsules, or keratin-coated pills, for ten days. After an interval of one week this course should be repeated. The drug is excreted in the urine, and can be recognized by the oxyquinoline test (green colour with perchloride of iron). Quinoxyl in pill form (4 gr. each), acts best when acute symptoms of amœbiasis have been controlled by emetine. The maximum dose is four a day.

---

[1] The underlying idea of E.B.I. therapy is that emetine should reach the large intestine unabsorbed. This problem has never been properly solved. Tests for emetine in the urine should be performed after emetine has been given hypodermically or by the mouth. Similarly, fæces of patients taking various modifications of E.B.I. should be extracted. Snelling's reaction for emetine consists of adding a few drops of HCl to potassium chlorate, which, with emetine, gives an orange red colour which soon changes to violet.

[2] A somewhat similar compound is iodochloroxyquinoline or vioform, which has proved effective in monkey amœbiasis (Leake)

To obtain permanent therapeutic results, quinoxyl should be given as rectal injections (retention enema), as well as by the mouth. By this method it exerts an effective amœbicidal action. The bowel must first be washed out and cleared of mucus by an enema (1 pint) of 2 per cent. sodium bicarbonate at 8 a.m. One hour later 227 c.c. (8 oz.) of a 2·5 per cent. solution of quinoxyl, in warm water, is introduced through a stout rectal tube. The patient should be encouraged to retain the solution as long as possible, from 8 to 10 hours. The solution is then returned as a greenish liquid containing mucus and débris derived from the bowel. The course of rectal injections is continued for ten days. The foot of the bed must be raised on blocks. The course may be repeated two or three times with a week's interval between each. Dieting and rest in bed are absolutely necessary. In resistant cases higher concentrations, up to 3·5 per cent. of quinoxyl, can be given by retention enemata.

IV. Combined synergic treatment.—In the Editor's opinion this method of treatment gives far the most satisfactory and permanent results. He has tested it out now in over 600 cases of proven intestinal amœbiasis during a period of twenty years. There have been two relapses in the series, both of which have been subsequently cured by further treatment. This treatment embodies the effects of quinoxyl and E.B.I. treatments given in combination. E.B.I. acts on the amœbic lesions in the upper portion of the large intestine, quinoxyl on ulcers and lesions situated in the lower portion. It is necessary that the patient should be *at rest* and *in bed* the whole of the ten days of this treatment. Due attention must be paid to the dietary. It is not necessary to give more than a total of 20 gr. of E.B.I. and the maximum individual dose should not exceed 2 gr.

SCHEME OF DIETARY AND COMBINED TREATMENT FOR INTESTINAL AMŒBIASIS

7 a.m., pot of tea and 2 oz. milk.
7.30 a.m., one egg, buttered toast, cup of tea and 2 oz. milk.
8 a.m., sodium-bicarbonate enema, 2 per cent., 1 pint.
8.30 a.m., quinoxyl 2½ per cent. by rectum (8 oz.).
9 a.m., 8 oz. milk.
10.30 a.m., juice of an orange, glucose ½ oz.
12 noon, liver soup, chicken or fish, toast, butter, custard or milk jelly, baked apple.
4 p.m., boiled egg, toast, butter, juice of one orange and ½ oz. glucose, grapes or ripe banana, sponge fingers.
5 p.m., quinoxyl enema voided.
6 p.m., 8 oz. milk ; bath.

9.30 p.m., sedative (luminal gr. 1).
10 p.m., E.B.I. (gr. 2).
10.30 p.m., sleep.
2 a.m., vomit (pharmacological action of E.B.I.).

During combined treatment the patient should be nursed in bed and should be allowed to get up for his bath. He may be allowed to use a night commode for stools and for voiding the residue of the quinoxyl enema. On the first night E.B.I., gr. 1, is given ; subsequently, gr. 2.

After the completion of treatment, the patient must be permitted two days' rest to regain his strength, as a sense of weakness or stiffness is produced in the limbs ; but, if carefully carried out, this treatment is not specially exhausting.

Medicinal treatment following the combined course.—An after-course of quinoxyl pills is prescribed, one or two at night for the next three weeks, according to the age and condition of the patient. These are good aperients and probably act by keeping the bowels relaxed. If the patient is much debilitated, one tablet of stovarsol is indicated daily, for 14 days.

Other methods of treatment.—*Stovarsol* (*Acetarsol*), an arsenical preparation (3-acetylamino-4-hydroxyphenyl-arsonic acid), containing 27·2 per cent. of arsenic, has been advocated, mainly in France, as an amœbicide, and has been widely used in the treatment of amœbic dysentery in combination with other drugs. It has a feeble amœbicidal action, but stimulating properties. Its special use is in the after-cure of amœbiasis. It is dispensed in 4-gr. tablets, but the maximum dose is two daily for one week to ten days, but not longer ; in sensitive persons not more than one tablet daily is advisable. This drug has to be carefully watched, as it may give rise to a toxic erythema with pyrexia resembling German measles, and even to exfoliative dermatitis. None of these arsenical drugs should be administered to patients in whom liver damage is suspected. A delayed papular toxic rash has been seen three weeks or so after the administration of the drug. Other varieties are known as *Spirocid*, *Orarsan* (Boots) and *Halarsol* (May & Baker).

Carbarsone (Eli Lilly & Co.), 4-carbamino-phenyl arsonic acid, ($H_2O_3AsC_6H_4$ $NHCONH_2$), was originally prepared by Ehrlich and contains 28·8 per cent. of arsenic. It has been much used in America and is given in the same manner as stovarsol, and has apparently the same therapeutic properties and the same indications. Most American authorities advise a dose of 0·25 grm. twice daily in capsules (pulvules) for ten days. Both stovarsol and carbarsone may be administered *per rectum* in the form of retention enemata of 2 grm. in 200 c.c. of warm 2 per cent. sodium bicarbonate solution. *Amibarson* is a similar compound. All these are useful in cyst-passer cases. Sodium amytal, 3 gr., is used as a sedative.

Kurchi and derivatives.—(*a*) Kurchi *bark* (containing an alkaloid, *conessine*) was formerly recommended, in 10 gr. tablets three times daily for a lengthy period, as after-treatment in intractable cases. It apparently has no specific action. (*b*) *Kurchinine hydrochloride* (Whiffen & Sons, Ltd.), a crystalline alkaloid from kurchi bark, has been used both for oral administration and hypodermic injections in doses of ½–1 gr. on three successive days. This has been supplanted by *Kurchi bismuthous iodide* (*Anabin*) which contains the total alkaloids of the bark. According to Acton and Chopra it was given by the mouth in 10 gr. doses, twice daily for ten days without producing deleterious effects. Although the first reports were encouraging, it is not much used at present.

Ko-sam, dispensed in tabloid form by Burroughs Wellcome, is prepared from the seeds of *Brucea sumatrana* and has a reputation in the Far East.

For resistant cases passing *E. histolytica* cysts, which are now occurring, Rhoads has successfully used *phenothiazine*—12 grm. suspended in 1½ pints of warm water, as a retention enema. Three treatments are given on alternate days and produce little or no discomfort.

Rivanol, a derivative of acridine, is injected *per rectum*, after a cleansing, non-irritating enema. It is diluted in distilled water 1 in 500 to 1 in 2000; of this 500-800 c.c. at body-temperature is administered *per rectum* with the patient lying on his side, or in the knee-elbow position. A course of ten or more treatments is necessary. Rivanol is antispasmodic and antiseptic and is useful for the relief of pain and tenesmus, especially in ulcerative colitis.

Vioform, or enterovioform (iodochlorhydroxyquinoline), is somewhat similar to iodoform and contains 37·5 per cent. of iodine. It is administered by the mouth in gelatin capsules each containing 0·25 grm. (4 gr.) of the powder, three times daily, for ten days. In chronic cases it may be injected for ten days as retention enemata, each consisting of 150–200 c.c. of warm water in which 2 tablets have been dissolved.

Diodoquin (5 : 7–diodo–8–hydroxy–quinoline) contains 63·9 per cent. iodine, and has acquired a great reputation in America. Its action is similar to that of vioform, but its absorption is more irregular and it is therefore more toxic. Tablets of 3·2 gr. are given by mouth, 10–12 a day for 20 days.

Of these preparations, carbasone and vioform have the best reputation in U.S.A. but are contra-indicated if there is any liver involvement.

Penicillin, in large doses, has a favourable effect on distressing, resistant and toxic cases, but none on the amœbæ.

Treatment of hepatitis.—During the course of amœbic dysentery, and for months afterwards, the liver must receive careful attention. It may not be possible to prevent abscess formation; but if pain suggests it, an attempt to avert this grave complication may be made by giving repeated doses of emetine subcutaneously, saline aperients, rest, low diet, fomentations, dry-cupping, and similar measures. Emetine acts much more rapidly and specifically in hepatitis than in amœbic infection of the bowel, and in some cases aspiration of the liver (hepatic phlebotomy) has a wonderful effect. Usually a total of 6 gr. of emetine suffices to overcome the more active symptoms.

Perforation of amœbic ulcer.—To avoid fatal peritonitis, diagnosis of perforation of the large bowel should be made as soon as possible. This is usually very difficult. Two successful instances during the 1914–18 war were recorded where timely operation saved the patient's life.

Other considerations.—Symptoms must be treated as they arise. Abdominal pain should be counteracted by hot applications, colic by a belladonna and bromide mixture (*see* p. 484), and tenesmus by morphia suppositories or starch-and-opium enemata.

Diet.—A suitable diet in the convalescent treatment of amœbic dysentery is important after the combined quinoxyl and E.B.I. treatment. Alcohol, unless taken in small quantities, certainly predisposes to relapse. The following diet is advocated for four weeks after active treatment:

Permitted.—Porridge; eggs; filleted or fried fish—haddock, plaice, cod, sole or whiting; toast or rusks; milk puddings—rice, sago, semolina, ground rice; spinach or young peas, vegetable marrow, cauliflower; plain cakes; fruit jellies; stewed pears or peaches; baked apples; bananas, grapes; tripe, brains, sweetbreads; chicken; rabbit; game.

Not permitted.—Cheese; new bread; potatoes; fats; suet puddings; rich cakes with raisins or spices; pastry; pickles.

Beverages.—Light wine only; no spirits, beer, or stout.
Meat.—Red meat, i.e., mutton or beef, can be permitted once daily.

Surgical measures must be reserved for complications of amœbiasis, e.g. pericolic abscess. Heroic procedures such as cæcostomy usually find no place in the treatment of intestinal amœbiasis.

Prophylaxis of amœbiasis is practically the same as for bacillary dysentery, and depends upon efficient sanitation, measures directed against the housefly, and avoidance of unboiled water, raw vegetables, or other foods which may have been contaminated by human fæces. As cysts of *E. histolytica* can only survive in a moist medium, there is a considerable amount of evidence, experimental and epidemiological, that amœbic infection is usually waterborne. The problem of dealing with human carriers of *E. histolytica* cysts is a constant difficulty. It is not likely to arise in countries equipped with a proper system of sanitation, but in no case ought a cyst-carrier to be employed as cook or mess orderly, or handle water supplies. Wherever possible, cyst-carriers should be treated by the combined method, though a prolonged course of carbarsone is sometimes effective.

Quinoxyl, in pill or tablet form (4 gr.) at night, in tropical countries where amœbiasis is rife appears to act as a prophylactic measure as well as a satisfactory aperient. Diodoquin is also recommended.

Efforts have been directed to exterminating amœbic cysts from contaminated water supplies. This cannot be done by medicating the water with chlorine or chloramine. Spector, Baylis and Gullans proved that the best method of removing the cysts is by filtration through sand-filters, combined with coagulation.

COMPLICATIONS OF AMŒBIASIS

1. HEPATIC ABSCESS (LIVER ABSCESS; HEPATIC AMŒBIASIS)

Geographical distribution.—Liver abscess of the type known as tropical abscess, for the most part a disease of warm climates, corresponds in its distribution with amœbiasis. While the entamœba is the principal element in its production, its incidence depends probably on special susceptibility of the European to this complication.

Ætiology. *Relation to amœbic dysentery.*—There can be no question of the existence of an intimate relationship between amœbic dysentery and liver abscess. Many well-authenticated statistics, as well as everyday experience, attest this. In 3,680 dysentery autopsies made in various tropical countries, and collated by Woodward, 779 (21 per cent.) revealed abscesses of the liver. Extensive amœbic ulceration may exist without exciting any subjective symptoms whatever (*see* p. 490). Moreover, many patients suffering from liver abscess forget, or fail to mention, a previous dysenteric attack, or may mislead the physician by describing such an attack as "diarrhœa," so that the relationship is much more intimate than even statistics indicate. In the great majority of cases dysentery antedates the abscess, it may be by as long as twenty years.

Race, sex, and climate.—Though common in Europeans in the tropics, liver abscess is proportionately rare among natives. Thus, in the native army of India the proportion of deaths from liver abscess to the total mortality in 1894 was only 0·6 per cent., whereas in the British army it was 7·4 per cent. Man for man, the relative liability of the European and the native soldier is as 95·2 to 4·8. This disproportion holds in spite of the fact that a larger proportion of the natives are infected with *E. histolytica.*

It is well known that European women in the tropics, though nearly as subject to dysentery as European men, rarely suffer from liver abscess, and children hardly ever. It is most common between the ages of 20 and 40, though there are records of amœbic abscesses of the liver in Egyptian children of three months of age and of others in India of ten. The youngest in the Editor's experience was an English girl of sixteen.

Pathology.—It may be inferred from the symptoms that in the early stages of suppurative hepatitis there is general congestion and enlargement of the liver; in some instances this condition may be more or less confined to one lobe or even part of a lobe. Later, as shown especially by observations on cases that have died from the attendant dysentery, one or more greyish, ill-defined, circular patches, ½–1 in. or thereabouts in diameter, are formed. These grey spots are very evident on section. A drop or two of a reddish, gummy pus may be expressed from these necrotic patches. Still later, the centres liquefy, and distinct but ragged abscess cavities are formed. An abscess thus commenced extends partly by breaking down of liver parenchyma; partly by more massive necrosis of portions of its wall; partly by the formation of additional foci of softening in the neighbourhood and subsequent breaking down of the intervening septa. The walls have a ragged and tessellated appearance. As the abscess enlarges, so the zone of necrotic tissue becomes narrower. The character of the contained pus also changes during the evolution of the abscess, and it frequently becomes secondarily infected with streptococci and other organisms, when it assumes a brownish or greenish colour.

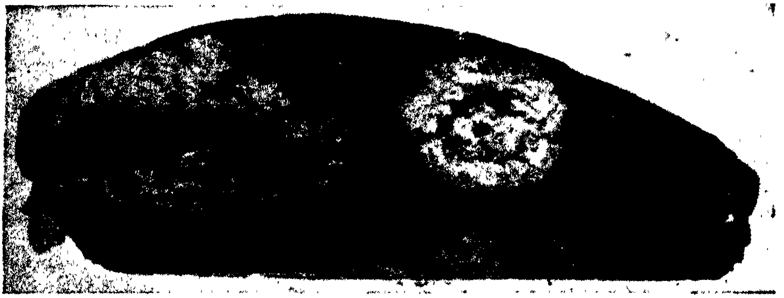
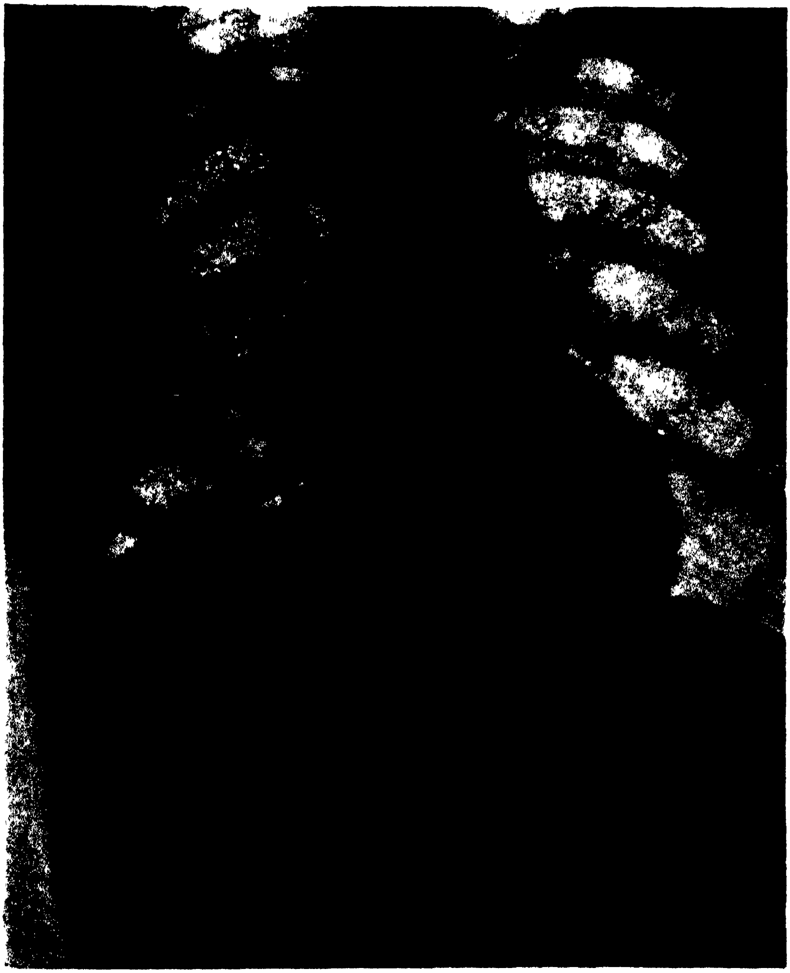


Fig. 72.—Multiple liver-abscesses from a case of acute amœbic dysentery, showing characteristic structure and zone of acute hyperæmia. Quarter nat. size.

Number, size, and situation of abscesses.—Liver abscess may be single or multiple. If multiple, there may be two, three, or many. When single, the abscess sometimes attains a great size. Frequently it is as large as a coco-nut, or even larger; the entire liver even, with the exception of a narrow zone of hepatic tissue, has been converted into a huge abscess sac. When multiple, the individual abscesses are generally smaller, ranging from the size of a filbert to that of an orange (Fig. 72).

As might be expected from considerations of the relative size of the parts, single abscess is much more common in the right than in the left smaller lobe. The upper part of the right lobe might be termed the seat of election.

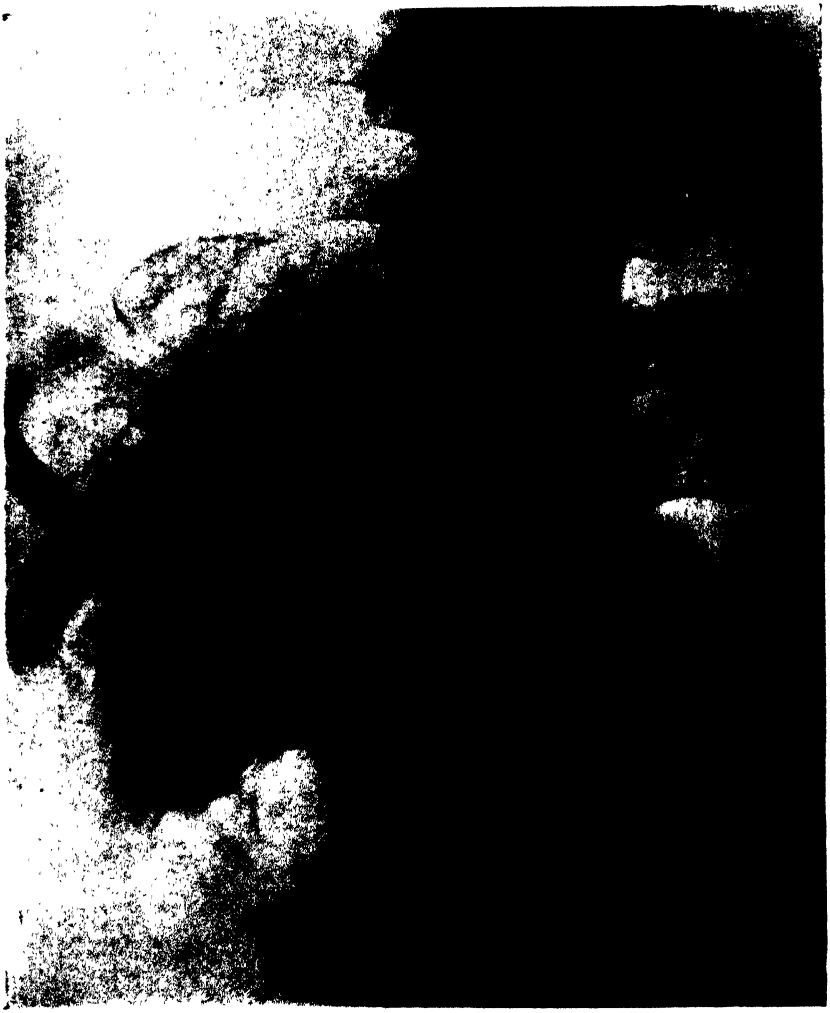


Radiograph of dome of diaphragm in liver abscess.

(Dr. Carmichael Low.)

LIVER ABSCESS.

PLATE XIV



Radiograph of cretified abscess in right lobe of liver.

(*Radiograph by Dr. M. Cordiner*)

LIVER ABSCESS.

Plate XV

Compensatory hypertrophy of the left lobe is commonly produced if there is great destruction of the right.

Adhesions to surrounding organs are frequently, though not invariably, formed as the abscess approaches the surface of the liver. In this way the danger of intraperitoneal extravasation is usually averted.

Intestinal ulceration usually co-exists; it may be very extensive, or confined to a few small punched-out ulcers, generally in the neighbourhood of the cæcum. Or, again, there may be no visible lesions of the mucous surface.

Pulmonary inflammation and abscess from escape of liver pus into the lungs are sometimes discovered *post mortem*. Generally the pulmonary abscess communicates with the mother abscess in the liver by a small opening in the diaphragm, the pleural sac being shut off by adhesions. (Plate XVI.)

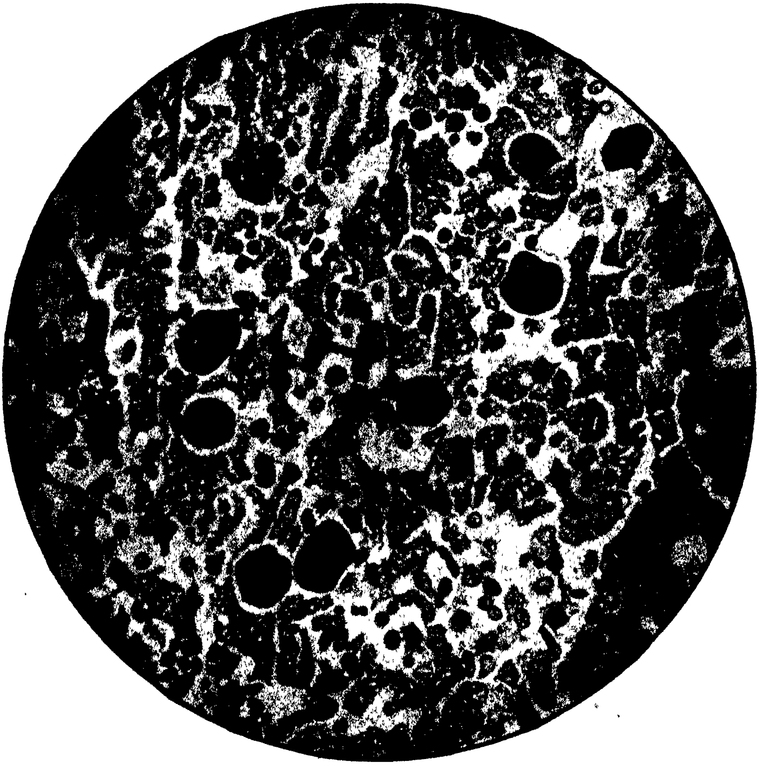


Fig. 73.—Microscopical section of liver abscess, showing *Entamœba* at margin of abscess cavity surrounded by necrotic liver cells.

Liver pus.—The naked-eye appearance of liver pus is peculiar, almost characteristic. When newly evacuated, it is usually chocolate-coloured, streaked, or mixed, with larger or smaller clots or streaks of blood, and here and there with streaks of clear mucoid yellowish material. It is so viscid that it will hardly soak into the dressings; it lies on the surface of the gauze like treacle on bread, spreading out between the skin and the dressing, and finding its way past the edge of the latter rather than penetrating it. When quite fresh, here and there little islands of what may be described as laudable pus may be made out in the brown mass. Sometimes it contains considerable pieces of necrotic tissue. Occasionally, also, from admixture of bile, the abscess contents are green-tinged; they are rarely offensive unless the abscess lies near the colon. Under the microscope many blood-corpuscles are seen, besides much broken-down liver tissue, large granular pigmented spherical cells, lecithin plaques, leucocytes, débris, oil globules, hæmatoidin, occasionally cholesterin, Charcot-Leyden crystals and sometimes a few entamœbæ. Cysts of *E. histolytica* are *never* found.

Entamœbæ and other organisms.—In Egypt, India, and elsewhere entamœbæ may be detected in half the cases. Usually they cannot be found in fresh liver pus, either aspirated or escaping during operation, but they appear, often in great profusion, four or five days later in discharges from the drainage-tube. They may occur in strings of eight to ten. Unless the patient is treated with emetine, the amœbæ may persist in the discharge until the abscess has healed. The Editor has succeeded in growing them on Drbohlav's selective medium when they were not apparent in the pus. The longer the abscess has persisted the larger its size, and the more difficult it is to find amœbæ (Fig. 73). The pus is bacteriologically sterile, but occasionally may become secondarily infected by *Bact. coli*, hæmolytic streptococci and *Bact. enteritidis.*

Encystment.—In rare instances liver abscess pus, instead of being chocolate-coloured and viscid, is yellow and creamy, particularly when the abscess becomes encysted. The walls are thick, smooth and fibrous. In the course of time the contents become cheesy, and ultimately cretified until the cyst shrivels up and contracts (*see* Plate XV). Calcified abscesses are occasionally found by radiography, and do not give rise to symptoms.

Bilaterality of the liver.—Until recently it was considered that no differences existed between the right and left branches of the portal vein, the hepatic artery and the hepatic ducts, although the right lobe of the liver is treble the size of the left. Cantlie in 1884 first noted hypertrophy of the left lobe of the liver consequent upon total destruction of the right. On this account, and also on account of the embryological development, it was suggested that the generally accepted anatomical division of the liver is incorrect and that it should be divided, not by the antero-posterior fissure, but by a line drawn from before backwards through the fundus of the gall-bladder to the spot where the anterior vena cava grooves the back of the liver; this is the mid-line of the liver. This view is borne out by pathological studies and the results of injection of the portal and hepatic veins and hepatic artery (McIndoe and Counseller). Copher and Dick (1928) demonstrated that the distribution of the portal streams in the liver of the dog can be determined by injections of trypan blue, and that there are at least three distinct and separate currents (streamline phenomena) in the portal vein. Hypertrophy of the left hepatic lobe ensues upon partial or complete destruction of the right, a feature of considerable importance in diagnosis.

The genesis of liver abscess.—Amœbic abscess of the liver appears to be the result of portal embolism from amœbic ulcers in the bowel. According to Rogers, the focus is usually in the right sector of the abdomen, either in the cæcum or ascending colon; this fact, therefore, accounts for the common situation of such an abscess in the right hepatic lobe. Direct infection of the anterior surface of the liver may possibly take place from an amœbic ulcer in the hepatic flexure, *via* the peritoneum, but there is no evidence to show that this constitutes the usual method. In *amœbic hepatitis*, which is probably the precursor of amœbic abscess, there appears to be a massive amœbic portal infection. Probably the great majority of the organisms are destroyed by resulting tissue-reaction; survivors multiply and cause necrosis of the surrounding liver cells and thus constitute the starting point of a liver abscess. Cytolysis is brought about by the rapidly multiplying amœbæ; but ultimately the amœbæ themselves are destroyed by the products of their own activity. Sterile amœbic abscesses at this stage are particularly liable to secondary infection with pyogenic organisms. As originally pointed out by Councilman and Lafleur, the primary lesion is central necrosis of the liver lobule, a prelude to subsequent abscess formation.

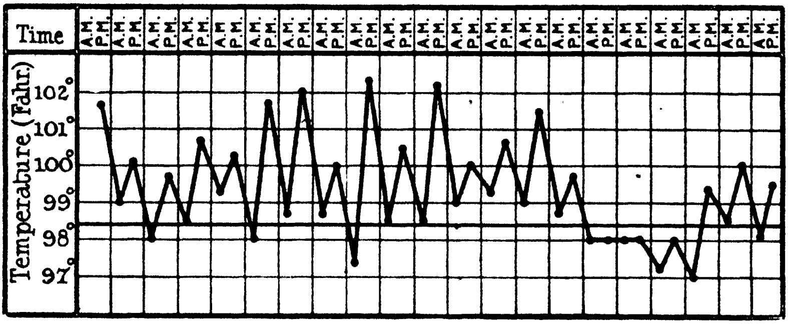


Chart 23.—Amœbic abscess of liver.

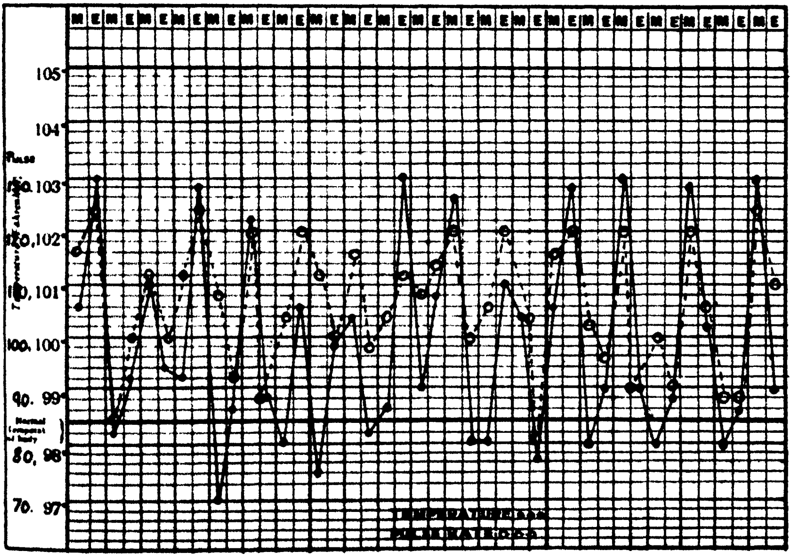


Chart 24.—Amœbic abscess of liver.

Hectic fever with tendency to tertian periodicity. Dotted line = pulse-rate.

Symptoms.—There is great variety in the symptoms of liver abscess. As a general rule, the patient is one who has long resided in the tropics and who may at some time or other have suffered from subacute attacks of dysentery. At first he becomes conscious of a sense of weight and fullness in the right hypochondrium, and later suffers from sharp stabbing pains over the hepatic area, accentuated by coughing.

Shoulder pain.—In a considerable proportion of cases a sensation of uneasiness or rheumatic pain around the right shoulder-joint is complained of, especially at night. Usually this is referred to the acromial region (appropriately termed, "the liver wing"). It is due to reflex irritation of the phrenic nerve, transmitted through the fourth cervical root from which the supra-acromial and supra-clavicular cutaneous nerves originate in the cervical plexus, and it is comparable to that of diaphragmatic pleurisy or gall-bladder disease. In left-lobe abscess pain is referred to the *left* shoulder-joint.

General features.—Soon the patient becomes feverish, particularly towards evening, and may experience a few short rigors. He begins to lose flesh, and his complexion assumes a yellow, muddy tinge. A quotidian fever now becomes a regular feature, every evening reaching 102° F., and sinking to below normal in the morning (Charts 23, 24). The pyrexial bouts are accompanied by profuse sweats, necessitating frequent changing of clothing during the night. The patient is emaciated, his tongue furred, the extremities cold and clammy; breathing is shallow and mainly thoracic. Sometimes an actual swelling in the epigastrium may be observed over the site of the abscess. Discomfort or deep-seated pain may be produced by palpation and deep percussion over the right hypochondrium. The lower border of the liver is usually enlarged below the costal margin; sometimes, but less frequently, it extends upwards an inch above the normal, while posteriorly the dullness can be detected from the angle of the scapula to the costal margin. It may be further observed that the upper line of dullness is arched, and is altered by changes in position, when the patient lies on his left side or when he stands up. Deep inspiration may give rise to acute pain, and sometimes one or two tender points may be discovered in the lower intercostal spaces. The spleen is not enlarged. On auscultation, pleuritic rubs may be detected at the base of the right lung, or signs of compression, such as inspiratory crepitations, decreased breath-sounds, or diminution of vocal fremitus may be noted at the base of the right lung (Fig. 74). Pain is usually relieved by lying on the affected side (Fig. 75).

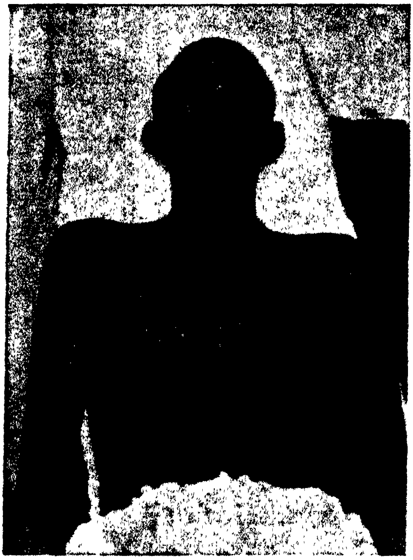


Fig. 74.—Clinical picture of liver abscess, showing enlargement of liver and bulging of chest wall.

In abscess of the left lobe a tumour of variable outline, sometimes resembling in shape and position an enlarged spleen, may be felt in the epi- or hypogastrium. Usually there is some compression involvement of the base of the left lung, but it must be remembered that such a tumour may arise from compensatory hypertrophy of the left lobe.

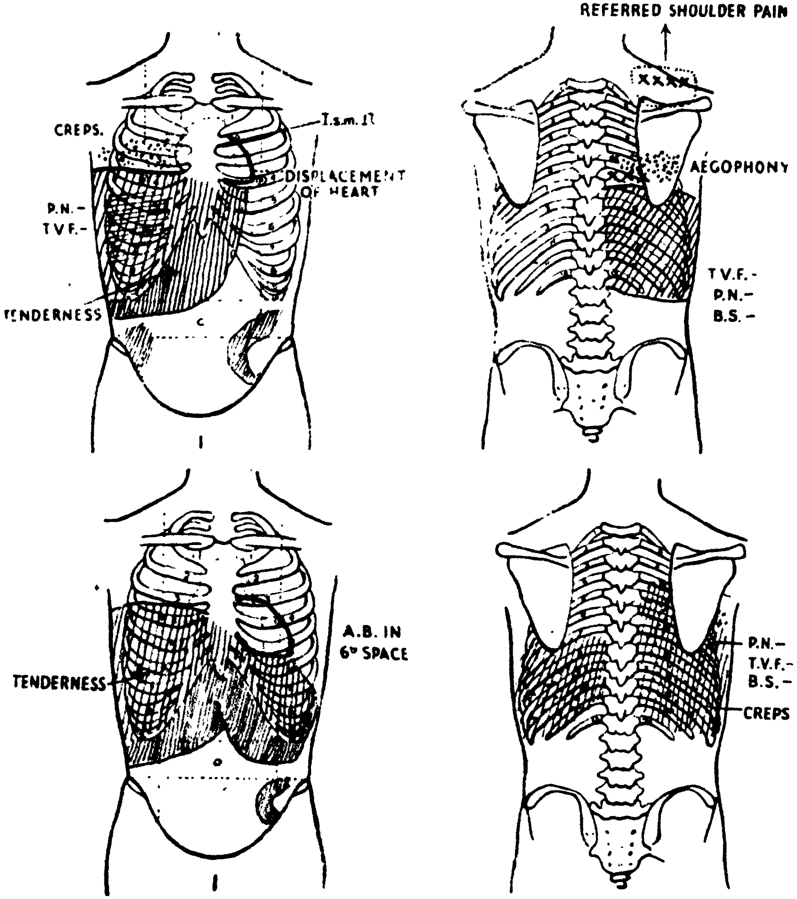


Fig. 75.—Physical signs of liver abscess.

Above—**Of right lobe of liver, cured by aspiration with Potain's aspirator** (6.7.25).

Leucocytes, 9,000 ; *E. histolytica* cysts in fæces. I s.m. II, basal systolic murmur ; P.N.—, percussion note diminished ; T.V.F.—, tactile vocal fremitus diminished ; B.S.—, breath-sounds absent ; CREPS., crepitations.

Below—**With hypertrophy of the left lobe, cured by aspiration of 65 ounces of sterile pus** (21.12.21).

Leucocytes, 12,000 ; *E. histolytica* cysts in fæces. A.B. apex-beat ; P.N.—, percussion note diminished ; T.V.F.—, tactile vocal fremitus diminished ; B.S.—, breath-sounds absent ; CREPS., crepitations.

As the case progresses, so the patient becomes more emaciated ; hectic with drenching nocturnal sweats continue ; liver dullness and increase ; or general enlargement may subside, and percussion reveal a local bulging in an upward or downward direction. If the abscess which has now formed is not relieved, the patient may die worn out after months of illness; or the abscess, having attained great dimensions, may burst into the right lung or pleura, or even elsewhere, and be discharged, with either recovery, or death from continued hectic fever and exhaustion or from some intercurrent complication. (Plate XVI.)

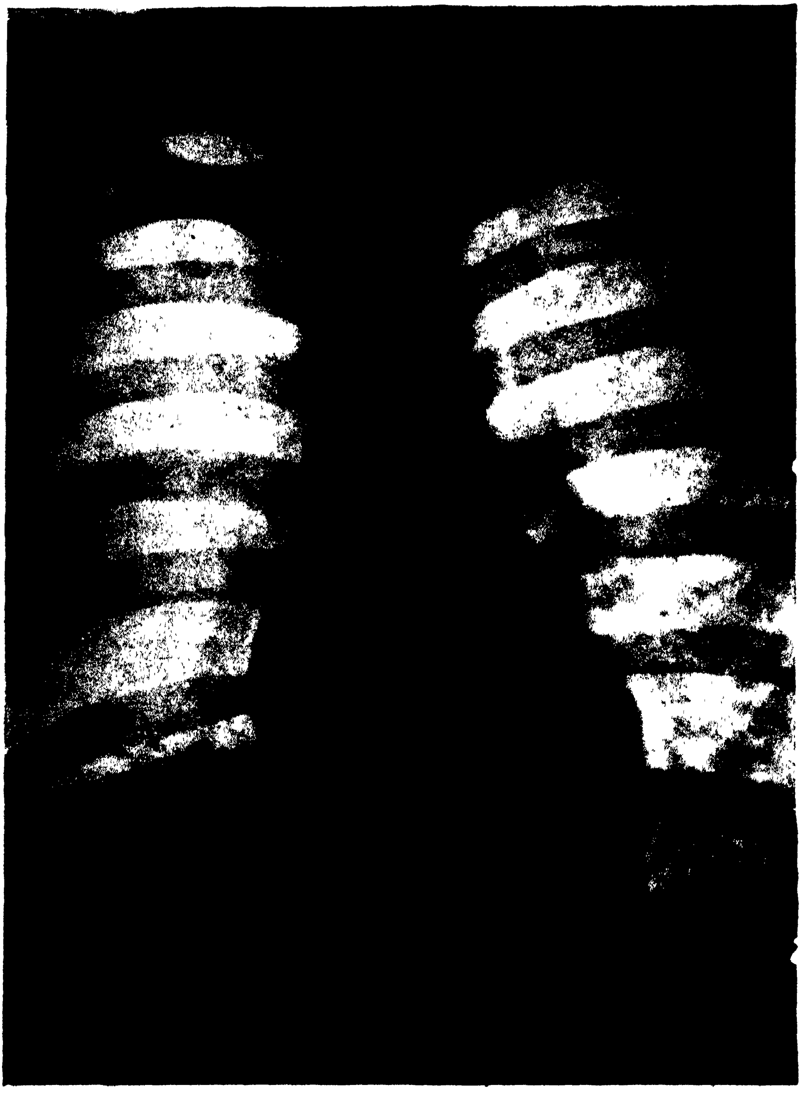
The blood shows a well-marked leucocytosis of 15,000–35,000, though in some rare cases there may be no appreciable rise. The mean average of the differential count in the Editor's series of cases is 70·8 per cent. polymorphonuclears; 22·2 per cent. lymphocytes; 6 per cent. large mononuclears; and 1 per cent. eosinophils. With liver abscess of long standing there is usually severe secondary anæmia, and occasionally the blood changes may assume features of the pernicious type.

In two exceptional cases of hepatic abscess recorded by the Editor the serum agglutinated *Bact. enteritidis* in high titre, with co-agglutination of *B. typhosum*, and the former organism was isolated from the abscess pus as well as from the fæces.

Great variety in the urgency of symptoms.—Although the foregoing is a fairly common history in liver abscess, there are many instances in which the initial symptoms are much more urgent and the disease progresses much more rapidly. In other instances subjective symptoms are almost entirely absent, or so subdued that the true nature of the case may be entirely misapprehended until the abscess bursts through the lung or bowel, or a fluctuating tumour appears in the neighbourhood of the liver; or, perhaps, until the unsuspected abscess is discovered on the post-mortem table.

Sometimes the initial fever is high, and persists for a considerable time, but later it usually becomes distinctly quotidian and intermittent; sometimes temperatures of 103° and 104° F. may be recorded. There is not one single cardinal sign which may not be absent in hepatic abscess; thus, large collections of pus have been noted unaccompanied by fever. Marked rigors are rare but, when present, indicate threatened rupture through the diaphragm or into some viscus. Sweating accompanying the pyrexia usually takes place about the head and neck. Enlarged cervical and axillary glands on the affected side may sometimes be noted, while rheumatic-like pains in, or swellings around joints, and clubbing of fingers have been described. Pain of some description is rarely absent. Usually, a sense of fullness and weight in the region of the liver, or maybe referred to the infrascapular region, is complained of; stabbing and stitch-like pains may be increased by pressure, and especially by deep inspiration or coughing. Localized painful areas usually occur below the costal margin, and indicate that the abscess is pointing in that direction. Pain on swallowing, when the bolus traverses the lower end of the œsophagus, has been recorded. Pain on firm pressure with the finger-tips in an intercostal space, and over a limited area, is a common and valuable localizing sign. Shoulder pain, in about one-sixth of the cases, may be the only symptom and may be noted before the advent of fever.

Attention may also be drawn to the respiratory symptoms; a painful cough, possibly due to reflex irritation of the diaphragm, may be prominent,



Radiograph of liver abscess bursting through the diaphragm into base of right lung, whence the pus is being evacuated through a branch of the right bronchus. A—collection of pus in pleural cavity; B—valve-shaped opening through diaphragm at site of abscess in liver. (*Radiograph by Dr. M. Berry.*)

LIVER ABSCESS.

PLATE XVI

while the respiration may be rapid and shallow. The patient usually lies on his back, inclining slightly to the affected side; if the abscess is on the right, lying on the *left* side becomes distressing owing to adhesions, or possibly to pressure on the heart.

The tongue is generally furred, the digestion disturbed; flatulence and diarrhœa are frequent. There may, but infrequently, be concurrent amœbic dysentery with blood and mucus in the stools.

The heart may be displaced laterally or upwards by pressure of a large abscess. Tachycardia and cardiac irregularities may result from toxic absorption or from pressure.

Rigidity of the upper part of the right rectus muscle may be noted if the abscess is situated in the vicinity of the gall-bladder. Percussion, besides eliciting tenderness and causing pain, may convey to the examiner a sensation of *ballottement* as of percussing a thick-walled elastic bag filled with air. The right upper superficial reflex may be diminished or absent.

Swellings in the epi- or hypogastrium closely simulate intra-abdominal tumours, and in apyrexial cases of hepatic abscess their nature may not be suspected until they have been aspirated. There may be varicosity of the epigastric veins. Local *œdema* over one or more intercostal spaces is sometimes apparent; local *bulging* usually indicates the site at which the abscess is pointing (Fig. 74).

Friction rubs, pleuritic or peritoneal, may sometimes be found; while pneumonic signs at the base of the right lung indicate contiguity of the abscess to the diaphragm. Œdema of the feet occurs in advanced cases.

The urine may contain albumin as the result of chronic pus-absorption. When considerable destruction of hepatic substance has taken place, the amount of urea is diminished and that of ammonia increased.

Jaundice is not by any means common; when intense it may be caused by pressure of the abscess on the bile canaliculi, or even the common bile duct. Quite commonly, however, there is latent icterus with slight yellow tingeing of the conjunctivæ.

The abscess may rupture into any contiguous organ, thereby producing spontaneous cure; generally it ruptures into the lung or pleura. When into the *lung*, the abscess contents may be suddenly coughed up in mouthfuls of frothy pus and blood: but usually this process is much more gradual and a few drachms are coughed up at a time, but in favourable cases the amount of expectoration gradually diminishes. Amœbic abscess of the lung—resulting from trans-diaphragmatic rupture—is apt to be mistaken for pulmonary tuberculosis. Amœbæ are only exceptionally found in the expectorated pus, but usually striated muscular fibres from the diaphragm may be recognized.

Expectorated liver-pus is usually characteristic, being chocolate-brown and particularly viscid.

Arrest of the discharge may not necessarily indicate recovery though cessation of the cough may be followed by rise of temperature and reappearance of night-sweats. Alternate emptying and refilling of the abscess cavity may recur many times before final recovery. In some cases expectoration never ceases, and is accompanied by other signs of pulmonary absorption, such as respiratory distress and clubbed fingers. Sudden rupture is often accompanied by the passage of melænic stools.

Rupture into the *pleura* may lead to pleural effusions, which may simulate empyema. Aspiration of these cases may yield clear yellow and highly albuminous pleuritic fluid. Pneumothorax may sometimes ensue.

Hepatic abscess may rupture into the *stomach*, causing vomiting of pus; into the *bowel*, causing diarrhœa and discharge of pus in the fæces; or, with fatal results, into the *pericardium* or *peritoneum*. Pericarditis, from close contact with intrahepatic suppuration, has also been recorded.

Rupture into the gall-bladder, bile-ducts, hepatic veins, portal veins, inferior vena cava and pelvis of the right kidney have also been reported.

Finally, spontaneous rupture may take place through the abdominal wall, and the abscess, by tracking along the round ligament, may empty itself. The surrounding skin may thus become infected with amœbæ.

From a study of 50 cases of amœbic abscess under the Editor's care it has been possible to set out the following table:—

	No. of patients.
History of previous dysentery	30
Entamœba histolytica or cysts in fæces	23
Shoulder pain, right	22
„ „ left	3
Pyrexia, intermittent	39
„ remittent typhoid-like	4
„ sudden onset, with rigors	2
Pyrexia absent	7
Night-sweats	40
Dysenteric infiltration of bowel—	
Sigmoid flexure	12
Cæcum and sigmoid	4
Enlargement of liver, upwards	12
„ „ downwards	38
Pain and tenderness in liver	24
Displacement of heart	4
Associated signs at base of right lung	38
Pleuritic rub	6
Rupture of abscess into lung	6

Mortality.—Formerly the case-mortality was high, 50–80 per cent., but at the present day, ipecacuanha and emetine, recognition of the intimate connection of liver abscess with amœbic dysentery, and improved methods for the evacuation of pus, have brought the mortality-rate to practically nothing. Death may be due to pressure on the abscess, to rupture and gangrene of the abscess-wall, to pneumothorax, to pneumonia, to associated dysentery, or to other intercurrent disease. Recovery may follow encystment or, possibly, absorption of the abscess.

Diagnosis.—Of all the grave tropical diseases, none is so frequently overlooked as abscess of the liver. Acute sthenic cases are readily enough recognized; not so insidious asthenic cases.

The most common mistakes in diagnosis are: (1) Failure to recognize the presence of disease of any description, even when an enormous abscess occupies the liver. (2) Misinterpretation of the significance and nature of a basal pneumonia—a condition often accompanying suppurative hepatitis. (3) Attributing the fever symptomatic of liver abscess to malaria. (4) Mistaking other diseases for abscess of the liver, and *vice versa*—for example, non-suppurative hepatitis, such as that attending malaria subtertian ; suppurative hepatitis before the formation of abscess ; syphilitic disease of the liver—softening gummata which are often attended with hectic fever ; pylephlebitis : suppurating hydatid ; suppurating actinomycosis ; gall-stone and inflammation of the gall-bladder ; subphrenic abscess due to ruptured gastric or duodenal ulcer, or appendix abscess ; abscess of the abdominal or thoracic wall ; pleurisy ; encysted empyema ; pyelitis of the right kidney ; bilharziasis ; scurvy and similar blood-diseases associated with hepatic enlargement ; ulcerative endocarditis ; kala-azar ; undulant fever ; trypanosomiasis, tuberculosis, and malignant disease. Any of these may be attended with fever of a hectic type, increased area of hepatic percussion dullness, and pain in or about the liver.

Differential diagnosis from suppurative cholecystitis without the aid of a " shadowcol " examination may be particularly difficult.

Cantlie originally classified pus in the neighbourhood of the liver into :—

(1) Suprahepatic abscess ;
(2) Intrahepatic abscess ;
(3) Infrahepatic or subhepatic abscess.

Suprahepatic abscess is not synonymous with " subdiaphragmatic abscess ; " it means the formation of pus between the layers of the broad ligament of the liver.

Frequently, a correct diagnosis can be reached only by repeated and careful study of the case in all its aspects. Golden rules in tropical practice are to think of hepatic abscess in all cases of progressive deterioration of health ; and to suspect it in all obscure abdominal cases associated with evening rise of temperature, particularly if there be an upward enlargement of or pain in the liver, leucocytosis, and a history of dysentery—not necessarily recent.

Low pneumonia of the right base in a tropical patient should always be regarded with suspicion, for it may mean abscess of the subjacent liver.

Perhaps the most common error is to regard the hectic fever of liver abscess as attributable to *malaria*. The regularity with which the daily fevers recur, the daily chilliness, or even rigor, coming on about the same hour, the profuse sweating, and other circumstances so compatible with a diagnosis of malaria, all contribute to this mistake. So common is the error that Osler declared he hardly ever met a case of liver abscess which had not been drenched with quinine. The periodicity of fever, and a polymorphonuclear leucocytosis should obviate so serious an error.

To mistake other forms of suppuration for liver abscess is not so serious, because in many suppurative diseases the treatment is the same as for liver abscess, and no bad result need follow if diagnosis is not quite accurate.

Intrahepatic suppuration may supervene in ascaris infection, in melioidosis (p. 282), in ascending pylephlebitis secondary to appendix abscess, in diverticulitis and, rarely, in infections with hæmolytic *Staphylococcus* *s*, or very exceptionally with bacillary dysentery. Suppurating abscesses have been reported secondary to duodenal ulceration and enteric infections. Carcinomatosis of the liver, unaccompanied by jaundice, may simulate amœbic abscess. A right perinephritic abscess may have to be considered. In subdiaphragmatic abscess caused by perforation of a-gastric or duodenal ulcer, an abdominal swelling can usually be recognized occupying a triangular area on the affected side. Gas is usually present and can be recognized by a resonance in the upper part which serves to distinguish it from liver abscess.

Pancreatic cyst elevating the left (less often the right) lobe of the liver may imitate an abscess, but it is not necessarily accompanied by fever.

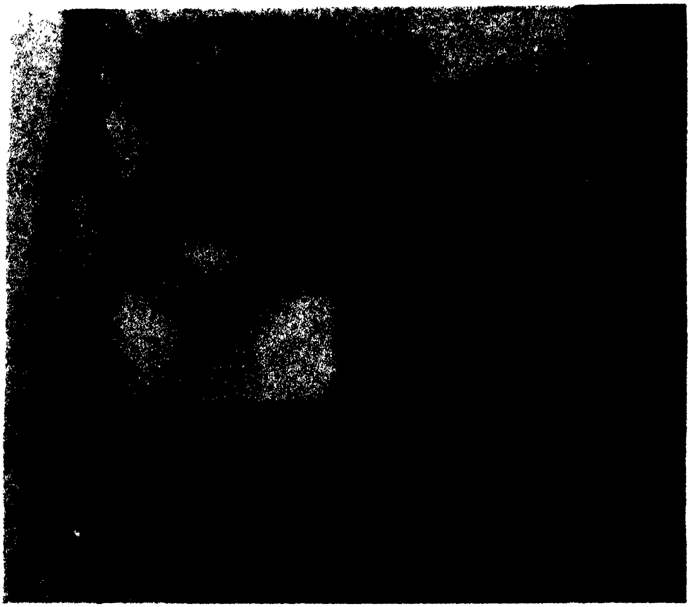


Fig. 76.—Visualization of amœbic liver abscess by puncture and injection of lipiodol in erect position. (*After* Snapper, "Chinese Lessons to Western Medicine.")

As a rule, it forms a definite tumour of considerable size in the left hypochondrium. Solitary non-parasitic cysts of the liver or polycystic disease may also have to be considered. Phantom tumour may give rise to difficulty, but this gradually disappears under a general anæsthetic.

A serious error is to overlook the presence of leucocythæmia, kala-azar pernicious anæmia or scurvy, and to proceed to aspirate an enlarged liver on the supposition that the symptoms arise from abscess.

Amœbic abscess of the liver which has ruptured through the diaphragm may have to be differentiated from many other pulmonary conditions, such as broncho-pneumonia, tuberculosis, actinomycosis, and malignant disease of the lung.

The presence of *Entamœba histolytica* cysts in the fæces is suggestive but by no means conclusive, of amœbic abscess. They are usually found in about 45 per cent. of all cases. Occasionally they may be cultured from the fæces in cases in which they are not visible under the microscope.

X-ray examination may confirm the upward enlargement in the liver, and bulging and " tenting " of the right dome of the diaphragm. Screening usually shows that it does not move on respiration (Plate XIV). Should, however, the abscess be situated in the centre of the liver, even if of considerable size, no definite information is usually obtainable by radiography except when the abscess has become partially encysted or calcified (Plate XV), when the outlines become apparent by X-ray. Occasionally, however, the outline of the liver abscess may show up as a more opaque area in the liver substance affording exact location for the exploring syringe. Occasionally, too, especially after inspiration, air, or possibly oxygen, appears in the abscess cavity and shows up the fluid level. Injection of air through the aspirating syringe has been practised with success, while lipiodol injection facilitates visualization (Fig. 76). The outline of the diaphragm is blurred when the abscess is near the upper surface of the liver. Normally the upper margin of the hepatic shadow forms a right angle with that of the vertebral column, but when abscess is present this may become more acute.

The bromsulphalein test, as an indication of hepatic disease and liver abscess has so far proved disappointing. The lævulose tolerance test is more satisfactory, especially if taken in association with decrease of plasma proteins and response of hypothrombinæmia to injections of vitamin K.

Diagnostic aspiration.—To make the diagnosis of liver abscess certain, aspiration must be performed. When the needle enters the liver, an up-and-down pendulum-like movement will be communicated to its outer extremity, in harmony with the rising and falling of the organ in respiration. If the needle does not exhibit this movement, its point may be in an abscess cavity, but such an abscess is not in the liver.

Prognosis.—The prognosis in early operations on single abscess of the liver, provided there is no dysentery or other complication, is good. In multiple abscess, or in single abscess, if there is active dysentery or other serious complication, the prognosis is bad ; if there are more than two or three abscesses, it is usually hopeless.

The *question of return to the tropics* after recovery from liver abscess frequently crops up. If feasible, and if the patient has not to make too great a sacrifice, he ought to remain in a temperate and healthy climate. There are many instances, however, of individuals who have enjoyed permanent good health in the tropics after recovery from liver abscess. Before return the bowel should be thoroughly cleansed of amœbic infection. Neglect of this precaution may lead to reinfection and recurrence seven years after the formation of the first abscess.

Treatment.—Hepatitis which has not proceeded to abscess-formation should be treated, especially if dysentery be present or has been antecedent, with full doses of emetine, repeated once or twice a day for two or three days or longer, by a cautious use of the purgative sulphates, and with poultices, rest, and low diet (*see* p. 502). Emetine should be injected in 1 gr. doses up to a total of 12 gr., and if cysts of *E. histolytica* are present in the stools, by a combined course of E.B.I. and quinoxyl. If there be much pain, relief may be afforded by either wet- or dry-cupping over the liver, or by leeches. Ammonium chloride, 20 gr. doses, three times daily, is commonly prescribed.

When rigor, or hectic fever, or local bulging, or persistent fever and local symptoms give ground for suspecting that abscess has formed, active medication must be suspended, and measures taken without unnecessary delay to locate the position of the pus by the aspirator.

Preliminary aspiration.—When he uses the aspirator the surgeon must be prepared to continue until all the pus is evacuated, or under exceptional circumstances, to operate.

Deep cocaine anæsthesia usually suffices, but nervous subjects should have gas and oxygen. A medium- or full-sized aspirator needle should be used, as the pus, owing to its viscidity, may not flow through a cannula of small bore.

If there are localizing signs, such as a tender spot, a fixed pain, localized œdema, localized pneumonic crepitus, pleuritic or peritoneal friction, these should be taken as indicating, with some probability, the seat of the abscess and the most promising spot for exploratory puncture. If none of these localizing signs is present, then, considering the fact that the majority of liver abscesses are situated in the upper and back part of the right lobe, the needle should, in the first instance, be inserted in the anterior axillary line in the 8th or 9th interspace. The needle should not be inserted more than 3¾ in. The distance of the inferior vena cava from any part of the chest wall is 4 in. The needle swings when the liver is engaged and, as it swings, it should be pushed gently forwards. The operator knows he is in the abscess cavity, because the needle is felt to pass into space. The syringe should then be affixed and aspiration commenced. Effusion of serum into the pleural cavity immediately adjacent to the liver abscess sometimes occurs.

In cases with cardiac or pulmonary embarrassment, aspiration can be efficiently carried out under local infiltration of skin and muscles with 2 per cent. novocain, to which is added 1 in 1000 adrenalin in the proportion of 10 drops to the ounce. The passage of the needle through the liver substance is painless. Should, however, the abscess point into the abdominal cavity, a general anæsthetic is advisable, for an open operation may become necessary. Occasionally the pus proves to be so thick that complete evacuation takes an hour or more; in these circumstances eusol in saline (half-strength) should be injected into the abscess cavity to dilute the pus.

An after course of combined emetine-bismuth-iodide and quinoxyl should be given to eradicate the amœbic infection from the bowel.

Open operations.—The indications for open operation are :—

(1) When after repeated aspiration no pus is obtained, but indications of its presence are too strong to be ignored.

(2) When an abscess points in the epigastrium, *i.e.*, is situated in the left lobe of the liver.

(3) When there is a large amount of pus which has been secondarily infected and has not yielded to treatment by aspiration.

The route for opening the thoracic or abdominal wall varies according to circumstances as follows :—

Transperitoneal route.—When pus is struck below the costal margin, the aspirator needle is left *in situ* and the abdomen is incised for a length of 3 in. (Kocher's incision), the intestines being guarded with packing. If adhesions are present, a sinus forceps is directed along the needle and pushed through into the abscess, and the blades are opened after withdrawal of the needle. The finger should be inserted into the abscess cavity. When the first gush of pus ceases, the exit is lightly plugged with gauze, the margins of the liver wound are carefully sutured to those of the parietal peritoneum, and the remainder of the wound closed. The gauze plug is now removed, and a wide drainage-tube, provided with a flange and lateral openings, is introduced to the bottom of the abscess cavity. Some surgeons use a wide-bore drainage tube, such as Tudor-Edwards empyema tube drain, pushed right to the bottom of the cavity to prevent extravasation.

Transpleural route.—Should the abscess be struck through an intercostal space, a couple of inches of (the 8th and 9th) ribs had better be resected. The diaphragm should then be stitched to the thoracic wall, or, better, to the skin as well, when the abscess may be opened with a forceps. An attempt should be made to stitch the capsule of the liver to the diaphragm. Should the pleura be opened, pneumothorax will result, but this is not necessarily serious. On no account should pus be permitted to enter the pleural cavity.

Sometimes it is simpler to expose the ribs and denude them of tissues. An iodine gauze pack should be inserted underneath the ribs and left for 3 to 4 days. Artificial adhesions are formed in the costophrenic sinus by a process of aseptic inflammation. Shears are then used to resect the ribs. Post-operative drainage is ensured by sinus forceps and a wide-bore tube. Dakin's solution may be used to irrigate as it exerts a solvent action on the liver abscess wall.

Treatment after operation.—For the first two days after a liver abscess has been opened the discharge is considerable, and the dressing may have to be changed frequently. Very soon, however, should the case do well, the discharge rapidly diminishes, and the dressing requires renewal only every other day, or every three or four days. During the first week the drainage-tube, provided it be acting efficiently, should not be disturbed, more particularly as it may be difficult to replace. Later, it may be removed and cleaned, and, when discharge has practically ceased, cautiously shortened. *It is a great mistake to begin shortening the tube before it is being pushed out, or so long as there is any appreciable discharge.* If there is the slightest indication, such as rise of temperature, that pus is being retained, the drainage must be rectified and the sinus, if necessary, dilated with forceps and finger, and a full-sized drainage-tube introduced as far as it will go. If this does not suffice, a counter-opening may have to be made. *Delay in remedying imperfect drainage is a serious—it may be fatal—error.*

Should an abscess be found septic, or should it become so, it must be flushed out daily, or twice a day, with a weak non-mercurial antiseptic, and a counter-opening made if necessary. Continuous drainage by the Carrel-Dakin tube method and daily eusol irrigation are often very successful. Where there is a thick necrotic zone delimiting the abscess, this continuous irrigation is highly necessary, and in order to dissolve the thick pus the injection of a ferment—enzymol (Fairchild) in the strength of 1 drachm to the ounce of water—is useful.

After a liver abscess has been opened and is draining well, temperature rapidly falls, and in a few days, or almost at once, becomes normal. Should fever persist, it is to be inferred either that the drainage is inefficient, or that there are more abscesses in the liver, or that there is some complication. If another abscess is suspected, it should be sought with the aspirator and, if found, drained.

It is advisable to give emetine in 1 gr. doses hypodermically, both before and after operation, and continue it for a fortnight, whichever operation is employed.

Discussion of the recognized methods of treatment of liver abscess.—The question is frequently and very reasonably asked why so many methods of treatment, medical as well as surgical, are employed in the treatment of liver abscess, and why some abscesses respond to injections of emetine while others are in no wise influenced by this drug. The answer appears to the Editor to be moderately simple. Aspiration of the abscess cavity by Potain's aspirator is the safest and most easily executed method. Sometimes more than one aspiration has to be carried out and an electric sucker may have to be employed. In the Editor's experience 28 per cent. of cases diagnosed as hepatic abscess resolve with emetine-therapy (12 gr.) followed by the E.B.I. and quinoxyl combined treatment. In these, probably, the formation of pus has not been extensive and the amœbæ are still active in the liver tissue. In 47 per cent., aspiration with Potain's aspirator, combined with emetine treatment, is successful. There still remains a proportion of cases (25 per cent.) in which open operation has to be resorted to, and emetine therapy has no appreciable effect whatever. These are the cases where either a large amount of pus is present or it is secondarily infected with streptococci or other organisms. It is disappointing to have to record that previous treatment of intestinal amœbiasis with E.B.I. and quinoxyl does not always prevent subsequent development of hepatic abscess.

Treatment of abscess discharging through the lung.—If an abscess is discharging through the lung and, although emetine has been freely administered, is not progressing favourably, the question of more efficient drainage by surgical means must be considered. There are two possibilities which render interference desirable: (*a*) Continued discharge of pus and blood, with or without attendant hectic fever—a condition which, if it persist, will, in all probability, in the end, kill the patient. (*b*) Not infrequently, prolonged discharge through the lung may induce fibrotic changes, pneumonia, or abscess with all its attendant dangers, such as thrombosis or abscess of the brain. (Plate XVI.)

In all cases of abscess discharging through the lung a careful register should be kept of three things—body-temperature, daily amount and character of expectoration, and, once a week, the weight. If temperature keeps up, if the amount of pus continues the same or increases, or if the patient continues to lose weight, an attempt should be made at all risks to reach and drain the abscess from the outside. If temperature remains normal, if pus gradually or intermittently decreases, and if the body-weight if maintained or increases, operation is unnecessary, or, at all events, should be deferred.

Medical treatment with full doses of ipecacuanha and emetine, maintained over a long period, generally exerts an almost miraculous effect and renders operative interference unnecessary.

In exploring the liver in such cases, it must be borne in mind that most likely the abscess cavity is collapsed, and that the sides of the abscess may be in contact. Such an abscess is not likely to be discovered unless the needle be thrust into its full extent and, whilst a good vacuum is being maintained in the aspirator, slowly withdrawn. If by good fortune the abscess has been traversed, then, when the end of the needle is crossing the cavity, a small amount of pus will be seen to flow.

Treatment of abscess rupturing into a serous cavity.—When there is evidence that an abscess of the liver has ruptured into the peritoneum, into the pleura, or into the pericardium, the particular serous cavity involved must be opened and at once treated on general surgical principles ; otherwise the patient will almost surely die. In the circumstances the surgeon will be justified in assuming great risks.

2. AMŒBIC ABSCESS OF THE BRAIN, SPLEEN AND EPIDIDYMIS

According to Armitage, 48 cases of amœbic abscess of the brain have been recorded, for the most part from Egypt. Like hepatic abscess, it is more common in men than in women. It is generally solitary, and may be regarded as a metastasis of hepatic abscess. The pressure symptoms resemble those of a cerebral tumour, and the abscess is invariably fatal. Amœbic abscess of the spleen was recorded by Rogers and others *post mortem*. Abscess of the epididymis was reported from China (Warthin).

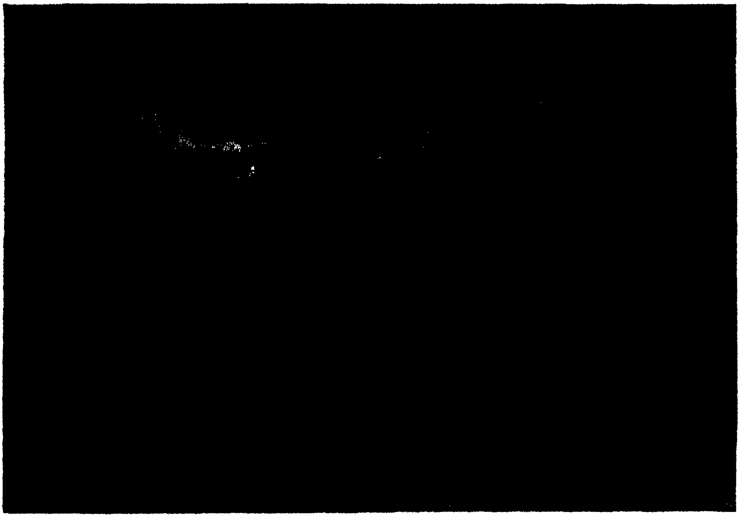


Fig. 77.—Amœbic granuloma and ulceration of abdominal parietes surrounding colostomy.

3. AMŒBIC INFECTION OF THE SKIN AND SUBCUTANEOUS TISSUES

Since 1892, it has been known that the skin may be subject to amœbic invasion in the vicinity of a discharging liver-abscess sinus. Amœbæ have been demonstrated in sections of the skin, and they are susceptible to emetine. Gangrenous lesions of the abdominal wall and perineum have been described from time to time, especially by Engman and Meleney (1931), while Hsu, in China, described a series of fourteen cases and showed that the condition is by no means rare. The Editor treated one such case, in which the parietes in the vicinity of a colostomy and the abdominal wall were involved (Fig. 77), with discharge of fœtid anchovy sauce pus. The patient was proved to have active amœbic dysentery. Extensive gangrenous destruction of the buttocks and skin of the back was seen in St. Mark's Hospital, London, in an ex-soldier who had served in India fifteen years previously; though he had never suffered from clinical dysentery, *E. histolytica* cysts were present in the fæces. The lower part of the rectum, the pelvic floor and the perineal tissues had been destroyed. Response to emetine therapy was quite remarkable. (Fig. 78).

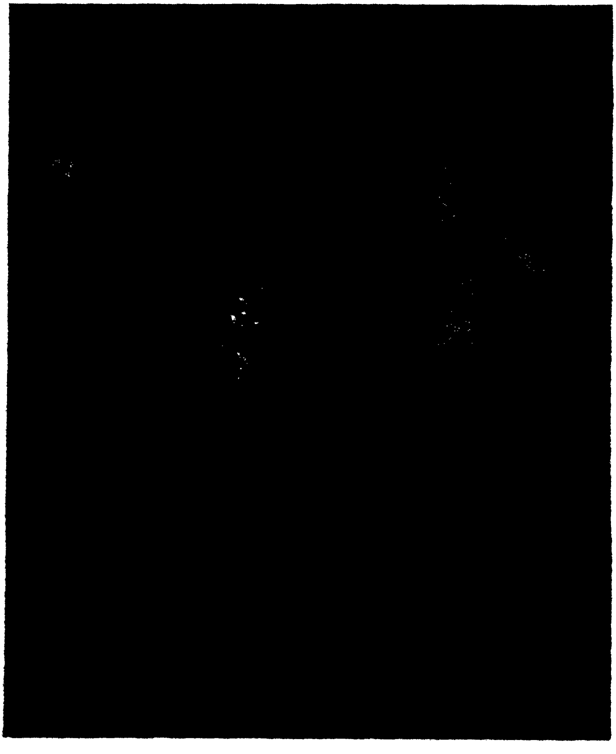


Fig. 78.—Amœbic ulceration of skin. Ulceration of sacrum, coccyx and perineum. (*W. B. Gabriel. Trans., Roy. Soc. Trop. Med.* j. 1933, 32 223.)

Amœbiasis cutis is a secondary infection of papillomata around the anus. The lesions have a punched-out appearance, and resemble in this respect intestinal amœbic lesions.

4. URINARY

A number of uncritical papers have appeared describing as amœbæ prostatic or other inflammatory cells which may be present in subacute cystitis or prostatitis. When *E. histolytica* in vegetative form is present in the urine it comes through a fistula between the bladder and the ulcerated rectum, as in the case reported by Craig (1911). Amœbic ulceration of the urethra in the male, as well as of the cervix uteri in the female, has been reported by Hsu in China, and amœbæ have been demonstrated in the tissues in microscopic sections; *E. histolytica* in the urine may be derived from this source.

5. PULMONARY AMŒBIASIS

This type of case is distinct from pulmonary abscess secondary to that of the liver where infection of the lung tissue results from direct extension of the hepatic abscess or by rupture into the bronchus.

In primary pulmonary amœbiasis the amœbæ reach the lung by direct embolism from the bowel. Having gained the pulmonary circulation, they form firm nodules, which later break down into small abscesses. The symptoms produced closely resemble those of a fugitive broncho-pneumonia, or some form of tuberculous infiltration.

These patients, who have been at some time the subjects of amœbic infection, suffer from pulmonary symptoms, with profuse purulent expectoration, sometimes tinged with blood, and respiratory distress with intermittent pyrexia. They are apt, however, to have rigors, which may serve to differentiate the condition from other respiratory diseases. The physical signs vary, but are usually those of broncho-pneumonic consolidation, detectable at the border of the scapula, especially on the right side. Skiagraphy may be of little avail in diagnosis. Amœbæ are not found in the sputum. There is, as a rule, a distinct leucocytosis. The response to emetine treatment is rapid and almost diagnostic (Chart 25). A full course of injections should be given.

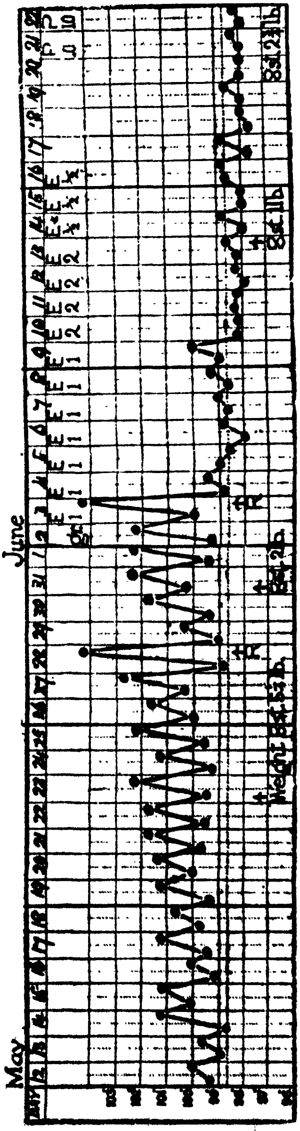


Chart 25.—Pulmonary amœbiasis with broncho-pneumonic symptoms and signs. Immediate improvement after institution of emetine treatment. (*Reproduced from "The Lancet."*)

BALANTIDIAL DYSENTERY

The occasional occurrence of *Balantidium coli* in the fæces, particularly in association with dysenteric diarrhœa, has been recognized for the last fifty years. It is only since Strong and Musgrave called attention to this subject that

Balantidium coli has come to be regarded as the germ cause of a particular type of colitis resembling in many respects amœbic dysentery. The parasite has been studied from the zoological standpoint, more especially in temperate climates, but it seems probable that extended observations will show that it is equally if not more prevalent in warm climates. It is a common parasite of the pig, and produces a fatal form of dysentery in monkeys in captivity and especially chimpanzees. Human cases have been reported all over the world, but especially from Germany and France, in those who tend domestic pigs. It is thought that cysts are transferred from the hands to the mouth during the handling of the intestines of infected animals. Mackenzie and Bean (1938) recorded the first case in England in a mental patient, and a second has been described.

How it attains the human intestine is not known, but as it is a common parasite of the pig, these animals should be regarded as the usual source of infection. Balantidium may live for a considerable time in water or fæces (one hour to three days). In liquid stools it exhibits great activity, indulging in locomotive as well as in rotary movements. For further description, *see* p. 877.

Geographical distribution.—Balantidiasis in man has been recorded from Russia, Scandinavia, Finland, Germany, France, Austria, Holland, Italy, Spain, Siberia, China (Tsingtau), Georgia, the Philippines, Cochin China, Andaman Islands, Sandwich Islands, Egypt, and the Sudan. Cases have also been reported from North America, North and South Carolina, Brazil, Porto Rico, Cuba and England.

Pathology.—There is little or nothing to distinguish the gross as well as the microscopic pathology from that of amœbic ulceration. The organisms have been found by Strong, Martini and Walker in the mesenteric glands. In thirty autopsies a variety of dysenteric lesions, from catarrhal congestion and diphtheritic patches to extensive ulceration, have been described. On section, Strong demonstrated the balantidium, not only in exudates on the surface of the bowel, but congregated in large numbers in the follicles, or embedded in the tissues forming the base of the ulcerations, including the submucosa and muscular coats, and even in the lumen of blood-vessels and lymphatics. The early lesions are minute hæmorrhages ; later, ulceration and abscesses appear. Bowman stated that the colon throughout its whole extent may be a mass of ulcers from which hang shreds of necrotic tissue—lesions resembling those of amœbic dysentery.

Symptoms.—These are, in the present state of knowledge, indistinguishable from those of amœbic dysentery. The disease is chronic, its special nature being discoverable only on microscopic examination of the stools. Generally, only one or two balantidia are found, but as many as twenty may be seen in every field of the microscope. The blood usually shows no change ; there is no leucocytosis and the polymorphonuclears represent 70 per cent. The ulcerations in the bowel, revealed by sigmoidoscopy, resemble those of intestinal amœbiasis as described by Mazza, Alvarado and Schürmann (1932). The mortality in 111 collected by Strong was 29 per cent.

Treatment.—Walker found that organic compounds of silver are effective in eradicating the infection. Thymol has been recommended, and oil of chenopodium, as in ancylostomiasis, has been reported to be successful. Young and Burrow (1943) cured seven cases with carbasone, 0·25 grm. twice daily for 10 days. This should be repeated if there is relapse. Yered tried a new remedy—carobinase—a watery extract of *Jacaranda decurrens*, 25 grm. in 500 c.c. of hot water, which is given as rectal lavage for three weeks. Methylene blue enemata, 2 pints of a 1 per cent. solution, are claimed to give good results. Westphal praises *Acranil*—hydrochlorate of acridine.

III. HELMINTHIC DYSENTERIES

Bilharzial dysentery.—Adeno-papillomata or ulcerations of the large intestine evoked by passage of eggs through the intestinal wall, are found in *Bilharzia mansoni*, *B. japonica*, and exceptionally in *B. hæmatobia* infections. The dysentery thus produced is met in those countries in which the parasites occur.

The stools contain yellow or bile-stained mucus with clots or streaks of blood, in which the bilharzia eggs can be found under a low power of the microscope. Eosinophilia associated with symptoms of dysentery is highly suggestive, and diagnosis should, if possible, be confirmed by the discovery of the characteristic eggs in the fæces. Sigmoidoscopic examination should help in doubtful cases. Pathologists should bear in mind that eggs are more easily found in the outer zone of solid fæces than in more central portions. Usually, pus cells in the fæces show a high proportion of eosinophils.

Infection with Œsophagostomum apiostomum and O. stephanostomum (p. 914).—These are rare intestinal parasites of man in Brazil, Northern Nigeria and Central Africa. When numerous they may give rise to dysenteric symptoms. The adult worms encyst under the submucosa, and may, together with their eggs, be recognized in the dysenteric discharges.

Infection with other helminthic parasites.—Chronic diarrhœa and possibly dysenteric attacks have occasionally been noted in intestinal infections with *Fasciolopsis buskii* (p 879), *Paragonimus westermanii* (p. 884), *Heterophyes heterophyes* (p. 883), and *Strongyloides stercoralis* (p. 917).

DIFFERENTIAL DIAGNOSIS OF THE DYSENTERIES

Mixed infections of different forms of dysentery may, of course, occur in those countries in which these diseases are endemic.

Combined infections of amœbic and bacillary dysentery are the most frequent. Such cases do not usually occur in temperate countries but during the course of severe epidemics of bacillary dysentery, when bacillary infection may be grafted upon some long-standing amœbic ulceration of the bowel. On the other hand, this dysentery may be followed by amœbic invasion of the bowel, which makes diagnosis still more difficult.

Bacillary dysentery occurs quite commonly as a terminal event in intestinal bilharziasis, and amœbic ulcers may sometimes be associated with the same condition.

Giardiasis.[1]—Of the intestinal flagellates which appear in the fæces, perhaps *Giardia* (*Lamblia*) *intestinalis* has the best claim to be regarded as pathogenic. The usual habitat of the parasite is in the upper part of the small intestine, but it may also heavily infest the duodenum. When newly passed in the fæces it is very active, presenting a characteristic appearance. During the passive stages cysts appear in the fæces in enormous numbers, and may be associated with those of *E. histolytica*. They are generally found in 4–16 per cent. of normal natives of the tropics. Other species are found in mammals and in reptiles, and one in the mouse, *Giardia muris*, is closely allied to the human parasite. In children in Northern countries giardia infection is three times as common as in adults. (In America 48·1 per cent. of industrial school children.) For a description of *G. intestinalis*, *see* p. 875.

---

[1] Giardiasis or lambliasis is mentioned in this section for the sake of completeness, although the diarrhœa associated with the parasite cannot strictly be classified as a dysentery.

In England and in Canada the parasite has been found in the intestine of quite a large number of normal children, while Boyd, Silverman, and others have shown that it can occasionally be demonstrated in the duodenal juice, bile, and gastric contents.

Some regard this parasite as pathogenic on the grounds that it is found in large numbers when the stools are liquid, and that quantities of mucus are passed containing active parasites.

Giardia infection is associated at times with a type of recurring diarrhœa accompanied by abdominal discomfort. The stools may be of a peculiar clay colour and pultaceous consistence, and may resemble those of sprue, or in English children of cœliac disease (R. Miller, 1926). Fat absorption has been found defective and excretion of bile below normal; both are attributed to mechanical effects of these parasites on the intestine. After these attacks, the encysted forms of *G. intestinalis* are present in large numbers in the fæces. Relapses tend to occur periodically, but eventually tolerance is acquired. Flatulence is almost invariable. In the acute stage the abdomen is tender and there is general discomfort. Véghelyi, who made observations on children in Budapest, described anorexia, headaches, dizziness, abdominal pains, and anæmia. The attack is not accompanied by emaciation, and symptoms probably originate from mechanical irritation, not from destruction of the mucosa, though in mice, in which similar parasites cause diarrhœa, they may penetrate the submucosa. Giardia infections are intractable and may persist for years. Hegner thought that the number of these parasites is dependent upon the diet as they tend to disappear from the fæces when the patient is fed on a protein dietary.

Treatment.—It is difficult to be certain of complete extirpation of these protozoa, for giardia frequently reappear in numbers in the fæces after an absence of several months. Apparently the parasite itself is subject to periods of great activity followed by periods of quiescence.

Atebrin (*mepacrine, quinacrine*) is specific both for the active phases of the parasite and for the cysts. This claim, originally put forward by L. Brumpt, has been abundantly confirmed from many sources. The parasites disappear from the fæces after a course of 0·1 grm. three times daily for 5–7 days, in adults; though in children two tablets daily suffice. Sometimes it may prove necessary to repeat the course. Probably giardia is mildly pathogenic, because associated symptoms also disappear after treatment. German and Scandinavian authorities prefer *Acranil*, the hydrochlorate of an acridine compound, in doses varying from 0.25 grm. daily for children under two, to 1·5 grm. daily for 5 days in those over ten. This drug is said to be more easily tolerated than atebrin.

OTHER FORMS OF DIARRHŒA AND DYSENTERY ASSOCIATED WITH INTESTINAL PARASITES

The common intestinal flagellates, *Trichomonas intestinalis* and *Chilomastix mesnili* (*see* pp. 872–874), though occurring commonly in diarrhœic and dysenteric stools, have little claim to pathogenicity. They are frequently present in large numbers in the fluid fæces of patients convalescing from bacillary or amœbic dysenteries. Probably the presence of large numbers of these flagellates in the bowel contents is due, to a great extent, to the fluid medium, in which they flourish ; but when a case of chronic diarrhœa is encountered and no other obvious signs can be found, and where large numbers of active flagellates are lashing about in liquid fæces, it becomes difficult not to assign some pathogenic properties to these apparent agents of disease. Hence the term **Flagellate Dysentery** has arisen—a term which probably indicates that the host has been exposed to abnormal intestinal infection. These organisms usually disappear after vigorous lavage of the bowel by irrigations of 2 per cent. sodium bicarbonate combined with stovarsol (gr. 4), or spirocid, in similar dose—two tablets daily for eight to ten days.

Spirochætal dysentery is attributed to the presence of numbers of spirochætes in the intestinal canal. These organisms, composed of three or more simple spirals, are known as *Spirochæta eurygyrata*, but they are not usually regarded as pathogenic.

Intestinal coccidiosis has to be considered, especially *Isospora hominis* (*see* p. 876), which causes diarrhœa, with mucus and Charcot-Leyden crystals in the fæces. Cases of this infection have been reported from all over the world, especially from the Near East and the Dutch East Indies.

Malarial dysentery.—A blood-stained discharge or, more frequently, hæmorrhage, may occur in the abdominal forms of subtertian malaria. The blood passed is very dark, due to petechial hæmorrhages from the intestinal mucosa. These are, as a rule, very serious cases. Instances were recorded by the Editor in which malaria was first suspected from discovery of the subtertian parasite within the red blood-corpuscles in the fæces. Besides the hæmorrhagic fæces, malaria should be suggested by the clinical aspect of the patient, sweating, icteric tint of sclerotics and skin, enlarged spleen. *Violent diarrhœa* may at times be the one outstanding clinical sign of an intensive subtertian infection.

Kala-azar dysentery.—Blood and mucus may be passed in the fæces in advanced cases of this disease, which may be due to an ulceration of the bowel by Leishman-Donovan bodies. The parasites are present in large numbers in the villi of the small intestines, and may form polypoid masses in the mucous membrane of the large intestine, whence they escape into the fæces.

Other conditions which may resemble dysentery.—There are other perhaps more familiar conditions, not necessarily of tropical origin, in which dysenteric symptoms may occur.

Of all common diseases with which mild dysentery may be confused, the first place must be given to *internal hæmorrhoids*. A correct diagnosis is readily made. Again, profuse offensive diarrhœic motions with blood and mucus may be passed in *tuberculous ulceration* of the large bowel, which may be comparatively common in the tropics. *Colitis*, ulcerative, membranous, or *hæmorrhagic*, resembles bacillary and amœbic dysenteries in clinical features and in the character of the stools, but can be differentiated by microscopic examination of the fæces, as well as by sigmoidoscopy. Idiopathic ulcerative colitis (colitis gravis) is becoming increasingly common and has to be differentiated from the bacillary dysenteries. It is undoubtedly a disease *sui generis* and is distinguished by pyrexia, toxæmia, intense anæmia, a tendency to spontaneous cure, and great liability to relapse. A very acute form sometimes follows cystoscopy, or instrumental investigation of the genito-urinary tract, and has been shown to be due to mercury poisoning from instruments sterilized with mercuric cyanide. *Mucous colitis*, or the syndrome which is commonly known by that name, is a frequent *sequel* of both bacillary and amœbic dysentery and is frequently confused with both. Stercoral ulceration, produced by chronic constipation associated with myxœdema, may give rise to a blood and mucous discharge. Certain surgical conditions—simple polypus, malignant disease, intussusception, even syphilitic disease of the rectum, or rectal stricture in lymphogranuloma inguinale (p. 624), the diagnosis of which should be determined by digital examination—must be kept in mind. *Polyposis* is a very distressing condition which usually undergoes malignant degeneration. Foreign body in the rectum is another possible diagnosis.

Blood and mucus are often passed in *diverticulitis*, which is quite common in tropical practice. In *paratyphoid B.* infections ulceration of the large intestine may give rise to blood and mucus in the stools. *Food poisoning* due to organisms of the Salmonella group may sometimes cause confusion by producing the same symptoms.

CHAPTER XXIX

TROPICAL SPRUE AND HILL DIARRHŒA

Synonyms.—Tropical Diarrhœa ; Aphthæ Tropicæ ; Psilosis ; Ceylon Sore Mouth.

Definition.—A peculiar and dangerous form of chronic inflammation of the whole or part of the mucous membrane of the alimentary canal. Although a disease of warm climates, it may develop for the first time in temperate countries, usually, however, in individuals who have previously resided in the tropics or subtropics.

History.—Sprue was first described by a Dutchman, V. Ketelaer, in 1669, and then by Hillary in Barbados in 1766, but the term " sprue " was first applied to the disease when it was rediscovered independently by Van der Burg in Java, and by Patrick Manson in Amoy, China, in 1880. Since that time, it has been found to be comparatively common in the tropics. A somewhat similar steatorrhœa was described by Thaysen in 1932 in northern Europe as " non-tropical sprue."

Geographical distribution.—South China, Manila, Cochin China, Japan, Java, the Straits Settlements, Ceylon, India, Mauritius, a few cases from Fiji, more frequently in the West Indies, the Southern United States, Porto Rico, Central America, the Guianas, and Queensland. Isolated cases have been recorded from Iraq, Egypt, Gibraltar and Palestine, Malta, North Africa and Russian Turkestan. In Central Africa the disease is rare, though the Editor has recorded one instance from Nyasaland.

Epidemiology and endemiology—Information so far on this subject suggests that sprue is a regional, as opposed to a climatic disease, and it pre-eminently affects Europeans. There was formerly doubt of its existence in native races ; highly pigmented people, usually the indigenous inhabitants of the endemic country, are less liable.

The disease is apt to occur in one or more members of the same family. Many instances of sprue in husband and wife have been recorded, probably from exposure to the same influences. Atmospheric temperature *per se* has no influence, for sprue originates at high altitudes in Ceylon and in the Himalayas, where the climate approximates to that of Europe.

There are residences in Bombay and bungalows in Ceylon which are notorious for the incidence of sprue in successive tenants ; these have been known as " sprue houses " and have given rise to a popular theory that the disease is connected in some way with " dry-rot " in wooden beams.

As a rule, sprue attacks those of middle age or over. Children are rarely affected, though there is one authentic record in an English boy from Ceylon of eleven years of age (Miller). Amongst Europeans both sexes appear equally liable.

Ætiology.—In spite of the considerable work which has been devoted to this subject, and the number of speculations which have been entertained, the true ætiology of tropical sprue remains obscure. The germ causation, as for instance, the yeast, or *Monilia* theory, has now been abandoned (Kohlbrugge, 1901, the Editor 1912). These organisms are regarded more as terminal and secondary invaders. Nutritional deficiency, as originally postulated by McCarrison, Elders and Nicholls, appears at present to be the most likely factor. There are cogent reasons for including sprue in the vitamin deficiency group, or at least regarding it as essentially the result of nutritional disorder. The modern discoveries on the ætiology of pellagra and the fact that in fully-developed tropical sprue there are signs and symptoms which may be ascribed to vitamin deficiency, mainly of the vitamin B_2 complex, have fortified this theory. But tropical sprue is undoubtedly a disease *sui generis*. The clinical characteristics are so typical as to admit no other assumption.

Biochemical studies, by Fairley and others, suggest that the phenomena of tropical sprue can best be explained in terms of a metabolic breakdown of the gastro-intestinal tract, characterized by defective absorption in the small intestine, primarily connected with defective secretion of Castle's intrinsic factor by the pyloric or Brünner's glands. The well accepted fact that the anæmia of sprue resembles that of pernicious anæmia, and responds in like manner to the extrinsic factor (in liver extracts), is certainly suggestive. Then there is the glossitis, which appears to bear the same significance as in pellagra, pernicious anæmia and idiopathic steatorrhœa, in all of which it seemingly represents the expression of B_2 avitaminosis and is influenced by administration of nicotinic acid and riboflavin (*see* p. 401).

Furthermore, as in pellagra, there is a pre-sprue, or larval condition, of which glossitis is the outstanding sign, which is indistinguishable from a similar stage in larval pellagra. A connecting link between sprue and pellagra is also suggested by the fact that pellagrous symptoms may sometimes be engrafted on sprue as a secondary phenomenon as in other forms of chronic steatorrhœa.

It has been suggested, with cogent arguments, that the sprue syndrome may be regarded as the expression of "*chronic jejuno-ileal insufficiency*" of which the outstanding signs are steatorrhœa, emaciation, meteorism, glossitis and megalocytic anæmia; and that these phenomena may be evoked by a number of conditions. The main argument for this view lies in the results of gastro-jejuno-colic fistula, which reproduce the main signs and symptoms of sprue; a similar clinical picture may be produced as the result of an ill-functioning gastro-enterostomy. Sprue-like signs and symptoms disappear when the defect is remedied by operation. Sprue symptoms may also supervene on resection of four feet, or more, of the lower ileum (Markoff), or may be produced by interference with chyle absorption in lymphadenomatous infiltration of the mesenteric glands, or by ulceration of the ileum.

Other diseases closely simulate tropical sprue, such as cœliac disease in children and idiopathic steatorrhœa in adults. These are probably the outcome of other forms of malabsorption from the small intestine. In idiopathic steatorrhœa the syndrome possibly represents an exaggerated phase of tropical sprue with implication of factors other than the vitamins of the B_2 complex. It is conceivable that the syndrome is produced, not so much by the absence of essential vitamins from the dietary, as by failure to absorb them.

These vitamins are probably necessary for proper absorption of fat by the villi of the small intestine, or intimately concerned with *phosphorylation*. Stannus has attempted to explain this complicated process as follows. The absorption of neutral fat in sprue is normal, but that of fatty acid, glycerol, cholesterin and glucose is defective, due to failure of *phosphorylation*, an essential process in absorption. The fact that neutral fat and glucose are normally absorbed without the aid of this process would explain the success of strawberry and banana diet in sprue. Calcium is deficient because it forms insoluble soaps with free fatty acids, and similarly there is a deficiency of phosphorus. The loss of calcium and fats, with their fat-soluble vitamins, is responsible for bone changes, tetany and failure of blood clotting. The mass of unabsorbed fatty acid and gas, due to fermentation of unabsorbed glucose, causes distension, and is responsible for the radiographic signs of sprue and sprue-like diseases (*see* p. 541). The physiological lesion in sprue is failure of *phosphorylation* due to defect of the enzyme system, the co-enzymes of which are members of the vitamin B complex—riboflavin, nicotinic acid, pyridoxine and probably others (*see* pp. 401–407).

Tropical sprue seems therefore to be coming into line with such other well-known avitaminoses as beriberi and pellagra in which a primary and secondary form may be recognized. For instance, the sprue syndrome may reveal itself as a primary disease, or as secondary to some other infection of the gastro-intestinal tract, such as bacillary dysentery.

That there are difficulties in accepting the nutritional theory *in toto* is not to be denied ; for instance, the restriction of tropical sprue to certain tropical and subtropical countries, and the fact that Europeans who develop the disease are usually better nourished than the indigenous inhabitants of the countries where sprue occurs. Moreover, Thaysen in 1932 described " non-tropical sprue " in Northern Europe which he claimed to be clinically and biochemically indistinguishable from the tropical form. Most of his cases were undoubtedly examples of idiopathic steatorrhœa, but there remained a residuum which correspond clinically to tropical sprue and are curable by the same methods. If further research should prove this to be the case, then sprue cannot be regarded as a strictly tropical disease. In the Editor's opinion, sprue is encountered in its most florid form in the tropics and subtropics, but minor manifestations of the sprue syndrome may be encountered in temperate zones. (*See* pp. 540–541).

These views may best be illustrated by the following table :—

Syndromes characterized by Glossitis and Stomatitis.

Ætiological factors.	*Syndrome.*	*Contributory factors.*
	Ariboflavinosis.	
1. Riboflavin deficiency.	Cheilosis, seborrhœic dermatitis, glossitis, corneal vascularization, keratitis, photophobia, conjunctivitis.	

Table—(*continued*).

Ætiological factors.	*Syndrome.*	*Contributory factors.*
	Pellagra.	
1. Nicotinic acid deficiency.	Glossitis, dermatitis. Changes in spinal cord.	Bacillary dysentery, amœbiasis, intestinal tuberculosis, alcoholism.
2. Riboflavin deficiency.	Stomatitis, glossitis, seborrhœic dermatitis.	Chronic gastro-intestinal disease, sprue.
	Tropical Sprue.	
1. Adrenal dysfunction ?	Low blood pressure.	Previous gastro-intestinal disease.
2. Riboflavin deficiency.	Stomatitis, conjunctivitis, "twilight-blindness."	
3. Deficiency of Vitamin B_2 complex.	Changes in spinal cord ?	
4. Deficiency of both factors of Castle.	Megalocytic anæmia.	
	Ideopathic Steatorrhœa.	
1. Congenital defect		Cœliac disease or "consumption bowels" in childhood.
2. Nicotinic acid deficiency ?	Glossitis, stomatitis.	
3. Riboflavin deficiency ?	Glossitis, stomatitis.	
4. Other factors in the Vitamin B_2 complex ?	Megacolon.	
5. Vitamin D deficiency.	Osteoporosis, hypocalcæmia.	
6. Factors of pernicious anæmia ?	Megalocytic anæmia.	
	Pernicious Anæmia. (*Addison's*).	
1. Deficiency of intrinsic factor of Castle.	Megalocytic anæmia.	
2. Deficiency of nicotinic acid and riboflavin ?	Glossitis.	
3. Deficiency of other factors in the B_2 complex ?	Changes in spinal cord.	
	Nutritional Megalocytic Anæmia.	
1. Deficiency of extrinsic factor.	Megalocytic anæmia.	Malaria, pregnancy.
2. Deficiency of riboflavin and nicotinic acid ?	Glossitis.	

In the majority of tropical sprue cases there is either hypo- or achlorhydria, sometimes even achylia gastrica, and Castle and Townsend have shown that the intrinsic factor is absent from the gastric juice, as in pernicious anæmia ; but the gastric element differs from that of pernicious anæmia in that acidity in sprue returns to normal after adequate treatment with liver extract and restoration of the patient to health.

Pathology.—The heart has usually undergone "brown atrophy." The liver is atrophied, and all the muscles and viscera are anæmic and wasted. With these exceptions and certain changes in the alimentary tract, so far as is known, there are no special lesions invariably associated with this disease. Occasionally, the pancreas shows fatty or granular degeneration of the cells, with softening of isolated acini and slight inflammatory infiltration of the connective tissue. These, however, are not more constant than are similar changes occasionally found in the liver and kidneys. Sections of the tongue show desquamation of the epithelium, especially from the surface of the fungiform papillæ.

Lesions of the alimentary tract.—In longstanding cases, there is usually atrophy of the small bowel so as to render it almost diaphanous. Ulceration and erosion of the ileum leading to perforation and peritonitis have been described by the Editor, but these, as well as the destruction of the intestinal villi, are now thought to be secondary changes (Mackie and N. H. Fairley, and, more recently, Thaysen). The chief lesions are thinning and atrophy of the mucous membrane of the absorptive and secretory epithelium with shrinkage of the villi. The changes are essentially those of degeneration and aplasia and there are evidences of blood destruction in the mucosa, suggesting absorption of some hæmolytic substance in the intestines and destruction of blood *in situ*. In autopsies, where death has been sudden, it is surprising indeed what few naked-eye changes can be seen. Pathological changes are seen in the red marrow of the femur and the tibia. This is usually reduced in quantity, though there may be hyperplasia, as in pernicious anæmia. It is suggested that in sprue there is a toxin which primarily stimulates, but eventually exhausts the hæmopoietic system. Ulceration of the ileum, leading to perforation and general peritonitis, may be the cause of death.

The messenteric glands may be enlarged, pigmented and fibrotic. The inflammatory changes in the mucosa and the invasion by round and plasma cells, formerly considered characteristic, are now held to be inconstant in appearance and extent, and possibly to be caused by the irritability brought about by acid fæces.

Clinical pathology.—The stools of sprue are characterized by their light colour and excessive size ; they may be five or six times the normal amount. Analysis reveals the ordinary elements of bile, notwithstanding the lack of colour. The excess of fat in the stools and low fat content of the blood (412·8 mgm. per cent.) indicate that a proportion is due to actual excretion of fat through the intestinal mucosa. (The normal is 600 mgm. per cent.). Normally, neutral fats in the fæces are to fatty acids in the proportion of 1 to 2 ; in pancreatic disease this ratio is reversed, and may be as high as 15 to 1 ; while in sprue stools more splitting of fats takes place, the proportion of neutral fats to fatty acids being as 1 to 3 or even 1 to 5. It is estimated that not uncommonly 50 grm. of fat is excreted in a single stool when the patient is living on a mixed dietary. The average results of fat analysis of fæces is as follows :—

Total fat	60	per cent.
Combined fatty acids	14	,, ,,
Free fatty acids ...	37	,, ,,
Unsoaped fat ...	45	,, ,,
Neutral fat	7	,, ,,

The trypsin and other enzyme activities in the stools are normal. These figures indicate that in sprue pancreatic digestion proceeds quite normally, but that the products of digestion are not absorbed, probably because the contents are hurried through the small intestine. Malabsorption of fats may probably be due to the same cause.

The blood picture of the fully-developed sprue case is a megalocytic anæmia, the size of the cells varying from 7·8–8 μ. The very variable degrees of anæmia coincide with the variable changes in the bone-marrow. As a general rule, this grave anæmia occurs in patients over fifty years of age. In no instance, in the cases investigated, has the colour index been less than 0·7. In the majority of cases it is above that figure. In uncomplicated sprue the leucocyte counts are either normal, or there is a leucopenia associated with a relative lymphocytosis. Blood crises commonly occur in sprue and are characterized by a rapid and critical fall in the hæmoglobin and red blood-corpuscles. Usually associated with severe diarrhœa, it progresses to a fatal issue, without remissions and without those evidences of blood regeneration which are so typical of similar crises in pernicious anæmia. Hyperbilirubinæmia is found more frequently in malaria and in pernicious anæmia than in sprue. (Van den Bergh test).

The Price-Jones curve resembles that of pernicious anæmia, being characterized by marked asymmetry, broadening of the base, displacement to the right, and a definite increase of the diameter of the corpuscles to 8·07 μ. It therefore seems that deficient blood-production rather than excessive blood-loss constitutes the basis of sprue anæmia.

Serum-calcium and phosphorus content.—Fairley, Mackie and others have confirmed Scott's observations that the ionic calcium is lowered in sprue, 7·4–9 mgm. per 100 c.c. of serum being constantly registered. Fairley and Bromfield, using Kramer and Tisdall's technique, found the average total calcium was 8·8 mgm. per cent. The average serum-phosphorus reading was 3·2 mgm. per 100 c.c. so that no rise above normal occurs. It is concluded that defective absorption is the basic factor involved in the low calcium content.

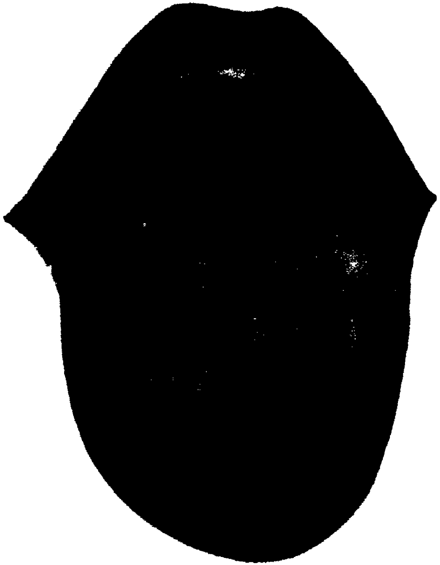
Blood cholesterol.—There is a definite hypocholesterolæmia, and Fairley has shown that the serum cholesterol averages 72·8 mgm. per 100 c.c., the lowest reading being about 40 mgm. The cholesterol content rises rapidly with liver-extract therapy and high-protein dietary.

Blood-sugar regulation.—Thaysen originally pointed out that in sprue, as well as in idiopathic steatorrhœa and cœliac disease, there is an abnormally low blood-sugar curve, which is not due to impairment of glucose absorption, or to its destruction in the intestines, but possibly is related to adrenal insufficiency.

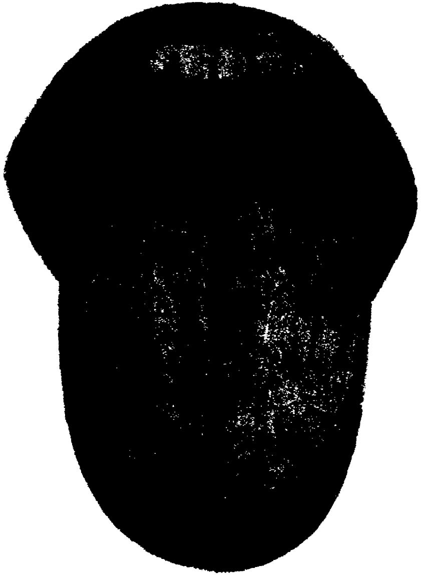
The urine is highly coloured, especially in cases with pronounced anæmia. This is due to the appearance of urobilinogen and urobilin in pathological amounts, derived from the products of blood destruction, as it is estimated that in sprue anæmia the blood-cells are being destroyed nearly five times more rapidly than normal. The diastatic reaction has been investigated and has been found to be well within the normal limits. This method affords a means by which sprue may be differentiated from chronic pancreatitis. In acute sprue there is porphyrinuria, as in pellagra.

Gastric secretion.—In most cases there is a relative hypochlorhydria or a normal acid curve, but occasionally hyperchlorhydria may be present. In cases with severe anæmia there is usually *achylia gastrica*.

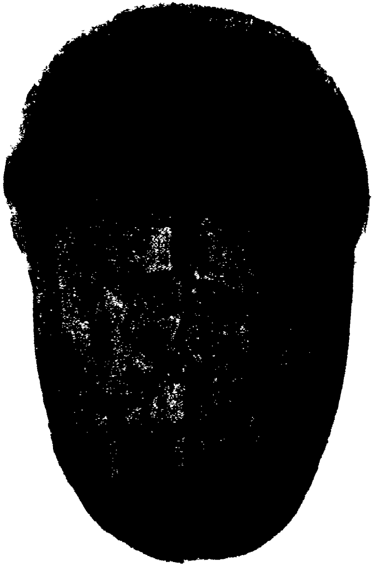
Symptoms. *Variability.*—There is infinite variety in the combination and in the severity of the various symptoms of sprue, as well as in the rate of progress of the disease. In some instances it may be almost a subacute process, running its course in a year or two; in others, again, it may drag on intermittently for ten or fifteen years. Much depends on the



Avitaminosis (B2) tongue (prepellagrous), showing angular stomatitis.



Acute stage of sprue with typical aphthæ.



Chronic sprue tongue.

(P. H. Manson-Bahr, del.)

PREPELLAGROUS AND SPRUE TONGUES.

Plate XVII

circumstances, the character, the care, the treatment, the age and the intelligence of the patient.

General symptoms in a typical case.—In an ordinary fully developed case the patient—who is generally dark or muddy in complexion and much emaciated—complains of three principal symptoms : soreness of the mouth, dyspeptic distension of the abdomen, and looseness of the bowels—the last being particularly urgent during the early morning and part of the forenoon. He may also complain of feeling physically weak, of loss of memory, and of inability to take exercise or to apply his mind. His friends will probably volunteer the information that he is irritable and unreasonable.

Mouth lesions.—The soreness depends on a variety of lesions of the mucous membrane, which, though painful, seem to be very superficial and vary considerably in intensity from day to day. During an exacerbation the tongue looks red and angry ; superficial erosions, patches of congestion, and perhaps minute vesicles appear on its surface, particularly about the edges and tip. Sometimes, from the folding consequent on swelling of the mucous membrane, its sides have the appearance of being fissured. The filiform papillæ cannot be made out, although here and there the fungiform stand out, pink and swollen (Plate XVII). If the patient be made to turn up the tip of the tongue, red patches of superficial erosion, sometimes covered with an aphthous-looking pellicle, may very likely be seen on either side of the frænum. These aphthæ probably form beneath the epithelium and subsequently burst. On eversion of the lips, similar patches and erosions are visible ; and, if the cheek be separated from the teeth, they may be seen on the buccal mucous membrane. Occasionally the palate is similarly affected ; very often, also, the mucous follicles are enlarged, shotty, and prominent. The gullet and uvula may also be congested and, in places, raw and sore.

In consequence of the irritation caused by these superficial and exceedingly sensitive lesions, the mouth tends to fill with a watery saliva, which may dribble from the corners. If the patient attempts to take any acrid food, strong wine, or anything except the very blandest diet, the pain and burning in the mouth are intolerable ; so much so that, although perhaps ravenously hungry, he shirks eating. Not infrequently, swallowing is accompanied and followed by a feeling of soreness and burning under the sternum, suggesting that the gullet, like the tongue, is also irritated, raw and tender. During exacerbations the condition of the mouth becomes greatly aggravated. Although during the temporary and occasional improvements it is much less painful, even then salt, spices, strong wines and all kinds of sapid foods sting unpleasantly ; and the tongue, particularly along its centre, is seen to be bare and polished as if brushed over with a coating of varnish. At all times the tongue is abnormally clean and devoid of fur ; during the exacerbations it is red and swollen ; but during the remissions, and when not inflamed, it is small and pointed, and, owing to the anæmic condition of the patient, it may be yellowish. The sore tongue and mouth may at first be the only signs, and they may persist for months or, it may be, for a year before complete sprue unfolds itself.

The tongue may be regarded as a mirror of the gastro-intestinal tract so that probably similar changes (hyperæmia and inflammation) are present in the stomach and small and large intestines. The mucosa of the rectum is inflamed, as the Editor has demonstrated by sigmoidoscopy.

Dyspepsia.—Dyspepsia is usually very troublesome, the feelings of weight, oppression, and gaseous distension after eating being sometimes excessive. Very likely the abdomen swells out like a drum, and unpleasant borborygmi roll through the bowel (Fig. 79). Occasionally, though not often, there may be vomiting, sometimes coming on suddenly, and not always accompanied by nausea. As a rule, there is a moderate hypochlorhydria, with adequate response to histamine, which may account for the dyspepsia. The gastroscopic appearances have been described as being similar to those of pernicious anæmia, and as taking the form of atrophic gastritis, which improves on intensive liver therapy.

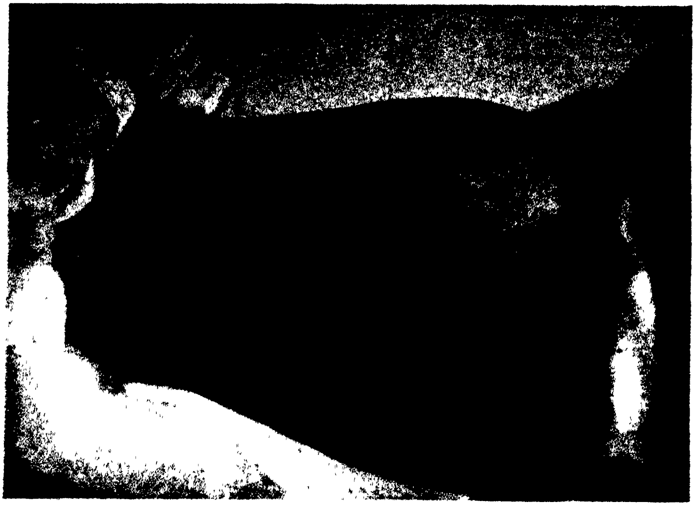


Fig. 79.—Sprue abdomen, showing intense meteorism, especially of lower quadrant.

Anæmia may be pronounced even in the early stages, though more generally it develops when diarrhœa has persisted for some time. It is a megalocytic, hyperchromic anæmia of the pernicious type, with alteration in the size and shape of the erythrocytes, very occasionally with normoblasts. Occasionally, severe anæmia, indistinguishable from that of Addisonian anæmia with high Van den Bergh readings, supervenes even when active sprue symptoms have disappeared.

Tetany associated with dilatation of the stomach is quite common in longstanding cases, but is also found in the early stages where there has been dehydration of the tissues and hypocalcæmia. It can often be elicited by compression of the upper arm (Trousseau's sign).

Cramps in hands and legs may be particularly distressing and are the accompaniments of hypocalcæmia.

Diarrhœa.—Diarrhœa associated with sprue is of two kinds: one chronic and habitual, the other more acute and, in the early stages, evanescent. The former is characterized by one or more daily discharges of a copious, pale, greyish, pasty, fermenting, acid, mawkish, evil-smelling material: the latter is watery, also pale and fermenting, the dejecta containing undigested food and, as a rule, an abnormally large amount of fat and fatty acids. In these latter circumstances diarrhœa usually brings with it considerable relief to the dyspeptic distension—at all events for a time. When the mouth is inflamed, diarrhœa is usually more active, but this is by no means invariable. The stools during periods of quiescence may be confined to one or two in the early morning or forenoon; during the later part of the day the patient is not disturbed. Even in this quiescent phase, however, they are always extraordinarily copious, the excessive bulk being attributable in great measure to fatty acids and to innumerable microscopic gas-bubbles. They are passed almost, or altogether, without pain. Not infrequently during exacerbations there may be a tender, excoriated condition of the anus, and sometimes, in women, a similar condition of the vagina, causing pruritus.

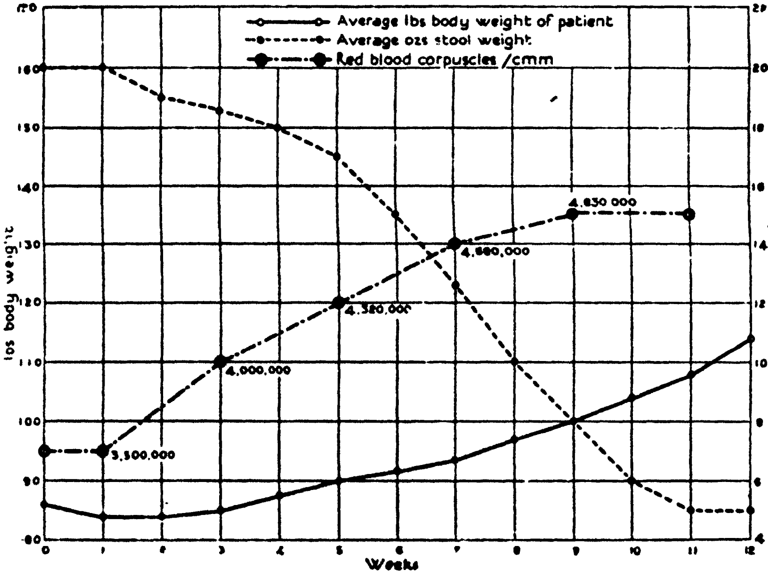


Chart 26.—Composite graph constructed from observations on ten cases, to show the relative increase in body-weight of patient and in red blood-corpuscles per cubic millimetre with coincident decrease in average weight of stool over the same period of treatment.

Types, history, course and termination. *Primary* or *protopathic sprue.*—There is a striking uniformity in the history of most cases of sprue. The patient has probably been suffering for months, or perhaps years, from irregularity of the bowels. This, the physician may be told, began, soon after arrival in the tropics, as a bilious morning diarrhœa. For a long time this morning diarrhœa went on, without interfering in any way with the general health. Later, the mouth now and again became tender, little blisters or excoriations appearing for a day or two at a time about the tip of the tongue or inside the lips. These sore spots would come and go. Perhaps, from time to time, exacerbations of the mouth symptoms would be associated with a little increase of diarrhœa. Gradually, the stools lost their bilious character and became pale and frothy; dyspeptic symptoms, particularly distension after meals, now appeared. As time went on, these symptoms would recur more frequently, and in a more pronounced form, following, almost inevitably, any little imprudence in food or exposure. The general condition now began to deteriorate; emaciation, langour, lassitude, and inability to get through the day's work satisfactorily, becoming more pronounced each summer until, finally, a condition of permanent invalidism was established.

Should the disease continue to progress, the emaciation advances slowly but surely. Diarrhœa may be almost constant, and now no longer confined to the morning hours; the complexion becomes dark, sometimes very dark; the appetite, at first in abeyance, may be ravenous, unusual indulgence in food being followed by increased discomfort, temporarily relieved by smart diarrhœa. At length the patient is confined to the house, perhaps to bed. The feet become œdematous, and the integuments hang like an ill-fitting garment, the details of the bony anatomy showing distinctly through the dry, scurfy, earthy skin. Finally, the patient dies in a semi-choleraic attack; or from inanition; or from some intercurrent disease. Such is the history of an ordinary, mismanaged case of sprue.

Another type of case commences as an acute entero-colitis or "hill diarrhœa," with sudden and profuse colicky diarrhœa, perhaps vomiting, and a certain amount of fever. The acute symptoms do not subside completely, but gradually acquire those of sprue grafted on to those of acute intestinal catarrh (*see* p. 589).

(*a*) *Gastric cases.*—Occasionally the morbid process is at first, judging from the existing clinical symptoms and subsequent history, confined to a limited part of the alimentary canal. Thus, there is sometimes sprue without diarrhœa, the principal symptoms being sore mouth, dyspeptic distension, pale, copious but solid stools, and wasting.

(*b*) *Intestinal cases.*—On the other hand, there are cases in which the mouth is not eroded and there is little or no distension or dyspepsia, but in which the stools are liquid, copious, pale, and frothy. Sometimes a patient, who may have suffered at an earlier period or on a former occasion from the first type of the disease, later acquires the diarrhœic form; and *vice versa.*

(*c*) *Sprue without diarrhœa.*—Sometimes under treatment the sore mouth, dyspepsia and diarrhœa completely subside; nevertheless, the wasting continues, the stools remaining phenomenally copious—so much so that the patient may declare that more is passed than has been eaten. In this case wasting is progressive, and the patient gradually dies of inanition.

(*d*) *Tongue or mouth sprue.*—As a rule, the characteristic appearance of the tongue is associated with gastric and intestinal symptoms, but this is not invariable. The Editor has described cases in Ceylon, and several others during the last twenty-five years, where the process remains confined to the mouth and gullet for one year or longer, before typical intestinal symptoms are noted. This stage may well be regarded as larval sprue.

Intestinal atrophy consequent on sprue.—In certain instances, under treatment the symptoms proper to sprue subside, but the patient's digestive and assimilative faculties are permanently impaired. Slight irregularities either in the quality or the amount of food, chill, fatigue, depressing emotions, and other trifling causes suffice to bring on dyspepsia accompanied by flatulence and diarrhœa. These cases may linger for years. Usually, they improve during the summer in England, getting worse during the winter and spring, or during cold damp weather. Ultimately, the patients die from general atrophy, diarrhœa, or some intercurrent disease.

Secondary sprue.—Sprue may follow closely on the heels of some other severe intestinal disease, such as amœbic or bacillary dysentery, or may be the direct sequel of hill diarrhœa. In bacillary dysentery, for instance, the sprue symptoms may be evanescent during convalescence, or, as sometimes happens, may become firmly established at some later period. Therefore, the recognition of a secondary form of sprue conforms with other nutritional diseases. The co-existence of intestinal amœbiasis with sprue has been recorded.

Sequelæ. *Anæmia and spinal symptoms.*—Severe anæmia of the pernicious type is a frequent sequel (*see* p. 534). Until recently it had been generally considered that sclerosis of the spinal cord did not occur in sprue and that this distinguished it in some degree from subacute combined degeneration of the cord in pernicious anæmia. But this distinction cannot be substantiated, for in longstanding cases of sprue with severe anæmia, occasionally unmistakable signs of cord involvement—spastic paraplegia, ankle-clonus, positive Babinski sign, and, eventually, complete and fatal paralysis of the lower extremities—have been observed. Neuritic signs in the arms and legs (pins and needles) frequently supervene; sometimes also *neuritis*, with paræsthesia and loss of reflexes, resembling beriberi, which has been found to respond satisfactorily to vitamin B_1 therapy.

Œdema.—Generalized œdema, especially of the legs, is a frequent accompaniment of sprue, especially in those patients who are responding to treatment.

Purpuric rash.—Petechial hæmorrhagic rashes, noticeable on the thighs and legs (Fig. 61, p. 445) are undoubtedly a scorbutic phenomenon and formerly occurred in patients who had been maintained on milk. This rash disappeared after the administration of adequate amounts of vitamin C. Small subcutaneous hæmorrhages on the hands are common in atrophic cases of sprue and probably are scorbutic.

Dermatitis.—A dermatitis is a frequent accompaniment of sprue, especially in elderly people with extreme anæmia. It generally breaks out during convalescence and when the patient is responding to treatment, and is mostly seen on the arms and chest. Sometimes the rash is pellagrous, and the Editor has recorded cases of association of this disease with sprue, where improvement occurred on the administration of nicotinic acid.

Special features of sprue in women.—Amenorrhœa and menstrual disturbances are extremely frequent in women with advanced sprue. Symptoms of sprue become exacerbated during pregnancy.

Relapses of sprue are unfortunately frequent and form a characteristic feature of this mysterious disease. Often they come on suddenly, and quite unexpectedly, without any apparent exciting cause. Sometimes, in the Editor's experience, typical relapses are observed after an interval of twenty years, and in one instance twenty-seven years, of apparently normal health in England.

Latency.—One of the most remarkable features of sprue is latency. Thus, it may arise in England in persons who have at some time resided in an endemic area of the disease. Usually, this period is one or two years; sometimes it is longer—seven or eight years; exceptionally it may be as long as twenty-five years.

Diagnosis.—The tongue, the stools, and the history seem sufficiently distinctive to render diagnosis easy. Nevertheless the Editor has known cases in which the disease has been diagnosed and treated as syphilis, the condition of the mouth being attributed to this disease, and the character of the stools and other symptoms ignored. Care must be exercised in interpreting the significance of the small area of liver dullness usually found in well-marked cases of sprue. This is not due to cirrhosis of the liver, but to its wasting, in common with other organs.

Differential diagnosis.—*Cœliac disease* (Gee's cœliac diarrhœa, or the Gee-Herter syndrome) occurs frequently in Europe in children under ten, and is also seen in those of European parentage returning from the tropics. Cœliac disease is probably congenital and its ætiology is therefore different from that of sprue, but the stools are similar in appearance and in chemical composition. This disease is associated with diarrhœa and meteorism, stunted growth, and incomplete sexual development. There is no involvement of the tongue and mouth, and the anæmia is not so severe as in tropical sprue. Symptoms usually disappear on a fat-free dietary. *Idiopathic steatorrhœa* is probably the same process as cœliac disease persisting in adult life, and was regarded by Thaysen in Denmark and Northern Europe as *non-tropical sprue.* This is a nutritional disturbance associated with tetany, osteomalacia and anæmia. It is therefore characterized by disturbances of the calcium metabolism and hypochromic anæmia. According to Bennett, Hunter and Vaughan, in " non-tropical sprue " there are often various cutaneous lesions, infantilism, megacolon, fine silky hair, brittleness and ridging of the nails, clubbed fingers, and a flattened type of blood-sugar curve after ingestion of glucose (which is also found in tropical sprue). Lens opacities, gross bony deformities, and tetany constitute the outward signs of defective calcium metabolism. The serum calcium is low and there is excessive excretion of fat. Both cœliac disease and idiopathic steatorrhœa may be complicated by secondary pellagra. An important, almost diagnostic, point of differentiation, is that these two forms of steatorrhœa do not respond to liver and vitamin therapy as does tropical sprue.

The absence of skin lesions and mental symptoms differentiates sprue from *pellagra.* The sprue tongue may be difficult to differentiate from that of pellagra ; the latter is pointed, and when it is inflamed and painful the process is generalized, not confined to certain definite and circumscribed areas as in sprue, and angular stomatitis is also often seen. The tongue of early pellagra (Plate XVII) is invariably associated with angular stomatitis and an atrophic condition of the lips (cheilosis). Atrophy of the lingual papillæ also occurs in pernicious anæmia and so this may be confused with sprue. No great difficulty should be experienced in differentiating *Addison's disease* from sprue. *Gastro-jejuno-colic* fistula may give rise to symptoms simulating sprue, but these disappear when appropriate surgical measures have been undertaken.

Giardiasis (*see* p. 525) may produce light-coloured fatty diarrhœa, and may be mistaken for sprue.

Differentiation of sprue from *chronic pancreatitis* may present difficulties. In the latter condition neutral fats predominate in the fæces, the tongue and mouth are not involved, and the diastatic reaction of the urine is high.

The low blood-sugar curve after the intake of 1 grm. of glucose per kilo. body weight serves to differentiate sprue from pernicious and allied *anæmias,* but a similar curve accompanies idiopathic steatorrhœa and cœliac disease. The anæmia of sprue greatly resembles that of pernicious anæmia, though normoblasts are rare and megaloblasts do not occur. High van den Bergh readings are the rule in true pernicious anæmia, exceptional in sprue. The differentiation from tropical macrocytic or nutritional anæmia cannot easily be made on blood examination alone, as the picture is very similar. This anæmia affects pregnant women in the tropics, and is not accompanied by diarrhœa.

Certain cases of *tabes mesenterica* may, on clinical grounds, resemble sprue, and so may disease of the *mesenteric glands,* such as lymphosarcoma or lymphadenoma.

The radiographic findings in sprue.—The Editor found no loss of tone in the stomach or intestines in acute incipient cases. The stomach is emptied in two hours after the barium meal, the hepatic flexure of the colon is reached in three hours, and the intestines are empty in 6–8 hours. In subacute cases there is slight loss of tone and vigour of peristalsis in the stomach. In chronic cases there is ballooning of the large intestine with some delay in the cæcum and colon. The herring-bone pattern in the jejunum described by American workers is not invariably observed as it is in idiopathic steatorrhœa.

Prognosis is good for recent cases, provided proper treatment is carried out. It is bad for patients over fifty, for longstanding cases, for careless and injudicious patients, and for those who cannot or will not take a special diet.

TREATMENT

General statement.—The treatment of sprue is mainly a matter of bodily rest and careful dieting in order to procure assimilation of the most easily absorbable foods. If treatment be undertaken sufficiently early, and be thoroughly and intelligently carried out, it is generally successful. Should, however, it be undertaken too late, when the glands and the absorbing surface of the alimentary canal have been hopelessly destroyed, the case is almost sure to end fatally. In prescribing treatment, therefore, the first thing is to get the patient thoroughly convinced of the serious nature of his complaint; for without his hearty and complete co-operation a well-established case will not be cured. To be successful, treatment must be thorough, sustained and prolonged. All predisposing causes, such as uterine or other discharges, syphilis, and helminthic infections must, of course, be removed as far as possible. The size and weight of the fæces should be estimated daily by weighing the pan and substracting from the total the known weight of the receptacle. The average daily weight of normal fæces is from six to eight ounces; in sprue it is commonly double or treble this amount. By keeping a chart of the average daily excretion, and by estimating the weight of the food ingested, an estimate may be formed of the daily intake and output.

Nursing of sprue cases is all-important. A great deal rests with the nurse; sprue patients are apt to be unreasonable and refractory, so she will need to be sympathetic and tactful, yet firm. A regular routine of feeding should be strictly adhered to, both in quantity and ingredients. The sheet anchor of treatment in sprue is diet, as all who have written on this disease agree. Fats and starches are not well assimilated.

Diet I.—The Editor is of the opinion that a combination of milk and protein meets the needs of most cases. If the tongue is very sore and the intestinal symptoms urgent, the patient is fed for the first week on a milk dietary and, if this is not easily tolerated, high protein milk—Sprulac (*see* p. 544). Sometimes, however, a mixture of milk and Sprulac may be given, or Benger's and Horlicks. When the intestinal symptoms have subsided, other ingredients may be added, as set out in the following tables:

TABLE I

First week.

Three pints of cow's milk (or Benger's Food) daily in 5-oz. feeds at two-hour intervals.

Toast, "pulled bread," rusks, with a small quantity of butter.

Total calorie value, about 1,100 calories.

TABLE II

Second week.

Three pints of milk (or Benger's Food) daily, as in Table I.

Rusks (Heudebert's or Verkade's "Groote Beschuit") and toast. Sago 6 oz.; liver soup, 12 oz. in two feeds of 6 oz. each.

One lightly boiled egg.

Weak tea or sprue tea (i.e. tea infused with milk in place of water) 8 oz.

Total calorie value, about 1,900 calories.

TABLE III

Third week and during convalescence.

Breakfast.—Porridge; 1 egg; toast (or rusks) and weak tea.

11 *a.m.*—Half a pint of warm milk, Sprulac or Benger's Food.

Lunch.—Liver soup, 12 oz.; chicken (minced), 6 oz.; spinach, 3 oz. (cauliflower, French beans, or vegetable marrow, 3½ oz.); sago or semolina pudding, 6 oz.; baked apple or banana, 6 oz.

Tea.—Toast; tea; Madeira cake, sponge cake, digestive biscuits, 3 oz.
Dinner.—Brain or sweetbread, 4 oz.; calves'-foot jelly, 3 oz.; banana, 3 oz.; arrowroot, 8 oz.
Total calorie value, about 3,900 calories.

This diet is given during the first week, with various medicinal measures; naturally it can be varied according to the needs and idiosyncrasies of each patient. The third table is instituted from the third week onwards and, during convalescence, for at least three or four months. It may be varied, of course, according to circumstances, and during the fruit season strawberries and raspberries may be added to the regimen.

In elderly patients (*i.e.*, those over 45) and where there is a high degree of anæmia, the addition of raw or underdone, finely shredded beef is of advantage.

Minced beef for Sprue Patients

8 oz. best beef;
1 good teaspoonful of marmite;
Pepper and salt;
2–3 tablespoonfuls of water.

Trim off all fat from the beef. Mince the raw beef finely, putting it twice through the mincing machine if necessary.

Place in double saucepan with marmite, seasoning, and water. Cook over boiling water, *stirring the ingredients with a fork all the time* until the meat has turned *brown and crumbly*—roughly 3 minutes.

Serve on a hot-water plate. Treated in this manner minced beef is a palatable dish.

Calorie value of 4 oz. is about 188.

In patients with flatulence and meteorism which are increased by milk, this beef diet may be substituted for one pint of milk.

Lightly-steamed meat with gravy is advantageous, and should be steamed in the following manner:

Take undercut of beef, 4 oz. Steam with 6 oz. of water for 5 to 7 minutes. Add a pinch of salt and serve as thick soup with lemon juice or slice of tomato.

The recipe for liver soup is as follows:

Take half a pound of calves' liver and cut it into small pieces. Place in a double saucepan, add ½ pint of cold water and simmer for 1½ hours. Strain through a sieve and add 1 pint of bone stock or chicken jelly, and, if necessary, flavour with marmite. Add a small quantity of pepper and salt.

Liver soup can be given in soup-platefuls of 8 oz. each, and may be taken together with underdone meat.

These methods, followed by carefully selected and increasing mixed diet, combined with warmth and rest, are the most successful ways of dealing with sprue. Food should never be given unless the patient is hungry. It is a great mistake to try to make these patients fat too rapidly, or to stimulate the desire for food by encouraging active exercise. The bowel is not in a condition to deal with large meals.

Diet 2. *High-protein dietary.*—This is especially indicated in elderly patients with inadequate assimilation, hypochlorhydria and anæmia. Alimentary rest in these cases is the therapeutic ideal and can be attained by feeding with a minimum amount of those food constituents with which the small intestine fails to deal adequately. Protein is the chief constituent, commencing with a low-calorie value and gradually increasing the quantity, while maintaining the high-protein rates. During this treatment five diets are ordered, the calorie value of which increases progressively from 770 in (*a*) to over 3,000 in (*e*), and the ratio of protein to fat and carbohydrate is maintained at 1·0 : 0·3 : 1·1.

(*a*) (Calorie value 770).

8 *a.m.*—Underdone beef, 3 oz.; juice of half an orange and glucose, 2 drachms.

12 *a.m.*—Soup, 4 oz.; underdone beef, 3 oz.; rusks, ¾ oz.; juice of half an orange and glucose, 1 drachm.

6 *p.m.*—Same as above.

(*b*) (Calorie value, 1,200).

The underdone beef is increased to 5 oz.; rusks and calves'-foot jelly added at 4 p.m. Tea, 10 oz.

(*c*).—Meals are given from 6 a.m.–7 p.m., as follows: 6 a.m., 8 a.m., 10 a.m., 12 a.m., 4 p.m., 7 p.m. The diet is much the same, with the addition of 10 oz. of tea with milk; three times daily, two baked apples and calves'-foot jelly.

(*d*) and (*e*).—The times are the same, but a greater quantity, up to 7 oz. of underdone beef is given twice daily. Bananas, custard and honey are introduced into the diet.

Protein milk diet.—As the result of biochemical investigations, it is now thought that flatulence and abdominal discomfort are in the main aggravated by fat in cow's milk. Fairley introduced a milk powder which combines the advantages of a high protein dietary with the bland properties of milk. This high-protein milk powder, or *Sprulac* (Cow & Gate Ltd.) is prepared from fresh milk which has been treated by passage through a gauze and wire filter, subsequently chilled, centrifuged to get rid of organic and inorganic débris, passed through a mechanical mixing apparatus and eventually desiccated at 120° C. The powder contains 10·6 per cent. fat; 34·0 per cent. protein and 45·0 per cent. lactose. The calorie value per ounce is 125 and the ratio of protein, fat and carbohydrate is 1·0: 0·3: 1·3. Sprulac can be given in the same manner as milk. One ounce of Sprulac is made up to 8 oz. with water and given every 2¼ hours for six feeds. Subsequently the amount may be increased and calves'-foot jelly and the juice of two oranges added. Sprulac forms an excellent addition to the diet in all stages of sprue.

Fruit diet.—The value of fruit in the treatment of sprue has long been recognized. Manson was in the habit of prescribing bananas and apples in sprue; often with marked success. Repeated trials of strawberries in sprue have to some extent confirmed their value. Bottled fruits, particularly peaches and pears, make suitable substitutes if strawberries or bananas are not obtainable. Of tinned fruits the most suitable are Libby's strawberries and blackberries, though it is doubtful whether preserved fruit possesses the same virtues as fresh. Fresh raspberries and blackberries are almost as well tolerated as strawberries. Fresh tomatoes are often beneficial. The bael fruit, or Bengal quince (*Ægle marmelos*), introduced by Fayrer in the treatment of this disease, seems to exert a beneficial effect in those countries (Ceylon and India) where it can be procured in a fresh state. During recent years it has been imported from the East on ice, and offered for sale in London. The ripe pulp can be scraped out of the hard exterior shell and eaten raw with sugar and cream, or made up with gelatin in a jelly. Two or three of these fruits may be given every day.

Return to Europe.—When sprue develops in the tropics, if feasible the patient should be sent to Europe as soon as possible. It is a mistake, however, to ship an invalid if the disease is active, or the end manifestly not far off. Diarrhœa should not be active when the patient is put on board ship. In every case provision should be made for continuation of the dietetic regimen and a supply of milk on board should be assured.

Clothing and general management.—Sprue patients returning to Europe ought to be especially careful in their clothing, and they ought to get out their warm clothes before the ship leaves the tropics. If they return during the winter, they should arrange to remain in the south of Europe until late spring. Next to an unsuitable dietary, perhaps cold is the most prejudicial influence to which a sprue case can be exposed. A sprue patient ought never to feel cold ; he ought always to wear thick flannels, thick stockings, and, when up and about, thick boots. In winter a chamois-leather sleeved waistcoat is of great service. His rooms ought to be warm. He ought to eat very sparingly. He ought never to be fatigued ; he ought to go to bed early and rise late ; in fact, he ought to do everything in his power to avoid irritating the bowel, to guard against chill, physiological depression, and copious eating.

During the summer England is suitable enough as a residence ; but during the cold winter and spring months some milder, drier and more sunny climate must be sought.

Sore tongue and mouth.—A great deal can be done to ameliorate the soreness and the dysphagia caused by ulceration of the tongue and mouth. The mouth should be kept very clean and washed out after each feed with a bland mouth-wash such as potassium chlorate, 1 drachm to the pint of hot water, but if the mouth is very painful, cocaine, 2 gr. to the ounce of glycerin and borax, brushed on to the tongue lightly before eating, will deaden sensibility. In certain cases where the saliva is very acid, as it generally is when the tongue is very raw, an alkaline mouth-wash should be used as follows :

Sod. bicarb.	gr.x (0·648 grm.)
Sod. biborate	gr.x (0·648 grm.)
Rose-water	℥iv (113·6 c.c.)

Diluted with water according to taste.

An efficient preparation for healing mouth lesions is an acriflavine dye, *Glauramine* (B.D.H.), of which the mouth-wash is made up of one teaspoonful (one drachm) to eight ounces of warm water. It temporarily stains the mouth and lips yellow. In some cases, especially where there is much sepsis, hydrogen-peroxide mouth-wash is useful. These measures should be combined with nicotinic acid and riboflavin, therapy, which undoubtedly help.

Specific treatment with vitamins.—In acute, as well as in chronic cases, the Editor has recorded success with nicotinic acid and riboflavin. Symptoms resolve in shorter time and the treatment is considerably curtailed.

Nicotinic acid is given in tablets (50 mgm.) in doses of 150–300 mgm. daily for three weeks or longer, reinforced, whenever glossitis and angular are acute, with *riboflavin*, 3 mgm. The immediate effects are in the subsidence of glossitis and rapid return of the taste-sense.

Abolition of these disagreeable phenomena exerts a profound influence on digestion and assimilation. Sometimes nicotinic acid produces a kind of histamine effect, with flushing of the face and throbbing of the arteries, but this soon passes off. This treatment also influences intestinal manifestations, but it is necessary that the diarrhœa should first be brought under control by rest in bed and suitable dietary and other measures. The most gratifying result is the abatement of flatulence and meteorism, which are usually so distressing and so persistent. It is probably wise to continue with nicotinic acid, in reservoir doses (50 mgm.), for three months or longer during convalescence.

In cases with marked hypochlorhydria the administration of hydrochloric acid is essential. A mixture containing 20 mm. of the dilute acid should be given before each main meal.

Diarrhœa.—The diarrhœa of sprue yields to dietetic treatment but, if excessive, the best method is to administer a small quantity of castor oil in teaspoonful doses, after which Batavia powder in the same quantity should be given, suspended in milk or water. If nocturnal diarrhœa is very severe, *chlorodyne* (10-15 min.) is often successful.

Batavia powder is a modification of "Peter Sys" specific (Shanghai) which was originally used by Manson and Cantlie in China. It is cuttle-fish bone combined with an iron compound. In some cases of diarrhœa during convalescence, it is advantageous to give it in wafer cachets, 15 gr., four times daily.

For less obstinate diarrhœa, Crooke's Collosol Lacto-Kaolin, in doses of one drachm daily, is recommended, while on occasions a bismuth and magnesia mixture (bism. oxycarb. 15 gr., mag. carb. pond. 15 gr. with sp. chlorof. et morph. co.) may be more suitable.

Anæmia.—No advance in the treatment of extreme cases of sprue has been so remarkable as blood-transfusion in patients in whom the anæmia resembles advanced pernicious anæmia. Some cases with a red cell count of 500,000 red cells to the c.mm. have recovered. Special precautions as regards blood groupings must be taken, and 300–400 c.c. of citrated blood injected intravenously. Sometimes two or three transfusions at weekly intervals are necessary. The modern drip-transfusion method is preferable.

The beneficial effects of liver soup in sprue have been noted since the early days of Manson and van der Burg. Since the discoveries of Minot and Murphy in 1926 it has been customary to reinforce soup by more potent liver extracts. The best are those of Eli Lilly, Parke Davis, and Oxo (Liveroid), but large quantities are required, and they are expensive. An important advance is intramuscular injection. In the Editor's hands. *Campolon* (Bayer), *Hepatex, Plexan* and *Examen* have been most efficient. In grave cases 4 c.c. is injected daily for six injections, but usually a series of 12 injections of 2 c.c. suffices. They should be made deep subcutaneously into the buttock, and are usually followed on the ninth or tenth day by a rise in the reticulocyte count. The first injections may be rather painful, but this gradually works off as more are given. Sometimes the addition of iron is of advantage, especially in cases without megalocytic blood changes. It may be given in the form of ferrous sulphate tablets (Glaxo) three times daily, or of *hæmatinic plastules* (Wyeth).

Flatulence and meteorism.—In cases with extreme distension injection of pituitary extract, especially *pitressin* (½–1 c.c.), is followed by passage of flatus and instant relief. Tablets of salol (10 gr.) and charcoal biscuits, or Charkaolin (Allen and Hanbury) in teaspoonful doses, are useful.

Constipation.—The constipation following the acute phase of sprue may be difficult to overcome. Often hard scybalæ form in the sigmoid colon and become impacted. The best aperient is castor oil. In extreme cases it may be necessary to give an enema of warm olive oil (10 oz.) and subsequently to remove the scybalæ from the rectum by the finger. As a general aperient, petrolagar (*red label*) or agarol is preferable to liquid paraffin.

Anal excoriation and irritation is sometimes a distressing feature, and may be relieved by the following ointment:

Orthoform		40 gr.
Zinc oxide		120 gr.
Starch		120 gr.
Paraffin	ad	1 oz.

Tetany and cramps.—The treatment of these symptoms, which are due to calcium deficiency, is by administration of calcium by the mouth in doses of 10 gr. three times daily, and in extreme cases by intravenous injection of salts, such as calcium gluconate (Sandoz) 10 c.c. or more.

To increase assimilation in atrophic cases.—Glucose, 2 oz. daily, should be added to the dietary throughout; and to increase assimilation when intestinal atrophy is a feature, *insulin*, 2–6 units, injected twice daily, may often be followed by an increase of the appetite and a corresponding aptitude for absorption.

Anorexia and vitamin B_1 deficiency.—The loss of appetite and taste in severe cases of sprue is a difficulty, but usually improves gradually when the patient is put to bed. It has been found that vitamin B_1 (aneurin) increases the desire for food; it may be injected, in doses of 25 mgm. daily, with advantage. It is curative also in cases presenting neuritic symptoms with loss of deep reflexes.

Hæmorrhages and scorbutic symptoms.—The Editor has treated two cases of purpuric rash resembling scurvy. This complication calls for vitamin C, either as ascorbic acid or as orange juice.

Additional methods of treatment.—Massage and passive movements are of benefit, especially in men who have been accustomed to exercise. Massage of the arms and legs should be instituted at once, but the abdomen should be left until the more urgent symptoms have subsided, when in constipated cases abdominal massage is of distinct value.

Heliotherapy and ultra-violet light radiations applied to chest and abdomen are very stimulating during convalescence in atonic and debilitated cases.

Convalescence.—Sprue patients, if possible, ought not to return to the tropics. Young adults often recover completely, but the danger of relapse is greatly enhanced in those over 50 if they return to the tropics, especially India. If compelled by circumstances to do so, they must exercise the utmost care for their health, and avoid exposure, cold baths, and all excesses; purge gently, and go on simple diet on the slightest sign of relapse. Alcohol, especially strong spirits, is strictly contra-indicated for

at least three months from the time of apparent recovery; light French wine may then be permitted.

Appended, as a guide for convalescent cases of sprue, is a diet table, which should be continued as long as possible.

Suggested Diet for Convalescent Cases of Sprue

Breakfast.
Well-boiled porridge (Quaker oats) or gruel. Sour milk (yoghourt).
Lightly boiled egg.
Toast, rusks or biscuits
Cocoa, weak tea,[1] or chocolate made with milk.
Butter in small quantities with toast or rusks.

a.m.
Warm milk or Sprulac, half a pint.

Clear liver soup, or chicken broth.
Chicken, preferably minced, boiled or roast.
Underdone minced beef.
Spinach, vegetable marrow, young peas, cauliflower, or French beans.
Milk puddings: sago, semolina.
Baked apple or banana.

Tea.
Weak tea.
Toast.
Wafers, water or Marie biscuits.
Madeira cake. Sponge fingers.

(Dinner should be the lightest meal of the day.)

Dinner (7 p.m.).
Brains.
Sweetbread.
Fruit or calves-foot jelly.
Arrowroot.

Fruits permitted.
Strawberries, commencing with maximum, 3 lb.
Raspberries, blackberries (as above).
Hot-house grapes.
Fruit jellies.
Bael fruit, bananas, oranges, papaya, tomatoes.
Ripe pears.

Articles of diet to be avoided.
Salmon, trout, mackerel, herrings.
Cheese.
Fresh bread.
Jams, especially marmalade.
Grease or fat.
Suet puddings.
Nuts.
Cakes with raisins.
Baked or fried potatoes.
Pastry.
Alcoholic drinks, especially spirits, gin, brandy and whisky.
Mineral waters.

Treatment of complications.—Careful search should be made for any co-existing infection from which the patient may be suffering. Malaria, especially benign tertian, and, more important still, syphilis, may prejudice recovery. Sprue patients with syphilis tolerate antisyphilitic treatment well and their general condition is benefited. Sprue may be complicated by amœbic dysentery, and in such cases vigorous treatment with emetine and emetine-bismuth-iodine may be necessary before any improvement in the general condition is noted. Acute appendicitis quite commonly complicates sprue and may necessitate operation, with the result that the underlying sprue is improved. Sometimes acute lobar pneumonia may supervene, and it has been noted that the sprue symptoms have been much improved after recovery.

Oral sepsis.—Carious teeth and pyorrhœa must be attended to after the subsidence of acute symptoms, but care should be exercised; it is a mistake to advocate too rapid extraction, as this is apt to provoke relapse.

---

[1] Sprue tea is best made with boiling milk in place of water.

HILL DIARRHŒA

Definition.—A form of morning diarrhœa accompanied by flatulent dyspepsia and the passage of copious liquid, pale, frothy stools. It occurs principally in Europeans on visiting the hills after residing for some time in the hot lowlands of tropical countries. Hill diarrhœa is a frequent precursor of the fully developed disease—sprue.

Geographical and seasonal distribution.—Crombie, who gave an excellent account of this disease in India, pointed out that a similar affection may show itself in the highlands of Europe, Africa, and possibly South America. Steen described a similar diarrhœa in Java, where it is known as "Bandoeng sprue." There is no reason, therefore, to suppose that hill diarrhœa is peculiar to India, although, owing to the large European population frequenting the hill sanatoria in that country, it has been particularly noticed there. An elevation of 6,000 feet or over, when combined with an atmosphere saturated with water vapour, is particularly favourable to its development. In India it is found to begin and end with the rains, during which, in certain years and places, it is apt to assume almost epidemic characters. Thus, during the wet season of 1880, in Simla, an epidemic of hill diarrhœa affected from 50 to 75 per cent. of the European population, three-fourths of the cases appearing within a week of each other. In some years hill diarrhœa is less prevalent than in others; but at the proper season few of the various hill sanatoria of India are without cases.

Ætiology and pathology.—It is difficult to say what may be the precise factors determining this disease. Low barometric pressure associated with great elevation above the sea-level may be a favouring circumstance. Damp seems to be indicated by the fact that the disease occurs principally during the rains. Chill after exposure to the high temperature of the plains has possibly an important share, but hill diarrhœa is certainly something more than an intestinal catarrh. There are no adequate grounds for connecting it with either the water or the food supply, though at one time Duncan advanced the hypothesis that mica in the drinking-water caused irritation of the intestinal mucosa. There is little doubt that it is in some way connected with sprue. Steen in Java suggested suprarenal insufficiency as the primary cause, but his views have not received much support.

Symptoms.—Without very obvious cause, the patient, who in other respects may be in good health, soon after arrival at a hill sanatorium becomes subject to a daily recurring diarrhœa, the looseness coming on regularly every morning some time between 3 and 5 o'clock. The calls to stool are apt to be sudden and imperative. The motions passed are remarkably copious; very watery in some instances, pasty in others. They are pale, frothy, and like recently stirred whitewash, so devoid are they of biliary colouring matter. Their passage is attended with little or no pain, often with a sense of relief. From one to half a dozen or more such stools may be voided before 11 a.m. After that hour—at all events, in ordinary cases—the diarrhœa is in abeyance for the rest of the day, and the patient may then go about his duties or pleasures without fear of inconvenience.

The distinctive features of this form of diarrhœa are, therefore, the regularity of its recurrence every morning and its cessation after a certain hour in the forenoon; the absence of colour in the stools; and the attendant flatulence. The abdomen is sometimes blown out like a drum, the patient being conscious of unpleasant borborygmi associated with a feeling as if some boiling or chemical operation were proceeding in his inside. Occasionally the stools are very pale

although there is no diarrhœa. A certain proportion of patients in whom symptoms persist develop the clinical picture of sprue.

Treatment.—The treatment recommended by Crombie, and endorsed by other medical men of experience in India, consists of a strict milk diet, rest, warm clothing, a teaspoonful of liquor hydrargyri perchloridi in water about fifteen minutes after food, and 12 gr. of pepsin, or a corresponding quantity of lactopeptin, two hours later. If, in spite of treatment, the disease persists, the patient must return to the low country.

CHAPTER XXX

INFANTILE CIRRHOSIS OF THE LIVER

A SPECIAL type of liver cirrhosis in Indian children was first described by Sen (1887). The disease appears to be peculiar to India, though a few similar cases have been reported from Mexico and North China. Cirrhosis of the liver of unknown ætiology is widespread in young adults in the tropics, especially in the East Indies (*see* p. 31).

This disease is prevalent in Hindu children. In Calcutta, from 1891 to 1893 inclusive, infantile biliary cirrhosis—the name given to the disease—caused 1,748 deaths. Although the Hindu and Mohammedan populations of that city are about equal, as many as 1,616 of the deaths occurred in Hindus, whilst only 80 occurred among Mohammedans, the balance of the mortality being among the Eurasians and other races. The disease occurs principally in children under one year, rarely attacking those over three years. Rao (1941) stated definitely that it most commonly occurs in children between the ages of six and twenty-four months, that it is not found in Moslems or Europeans, and that it occurs chiefly in vegetarian families. As a rule, it begins during dentition, or about the seventh or eighth month, running a fatal course in from three to eight months. In rare cases it may commence within a few days of birth. Instead of lasting several months, its progress may be much more rapid, and terminate in death in from two to three weeks. In India it is common in Bengal, Madras, Bombay Presidency, and the United Provinces ; it is more prevalent in rural districts than in towns.

Ætiology.—The cause of infantile cirrhosis is unknown. Neither alcohol, syphilis, nor malaria has anything to do with it. The children of the well-to-do are relatively more frequently attacked than those of the poor. It tends to run in families, child after child of the same parents succumbing within a year or two of birth. Mukerji remarked that the disease is especially apt to occur in grossly overfed and pampered children in Bengal, and has adduced evidence that the virus is probably conveyed by the mother's milk to the child. Green-Armytage believed the true ætiology to be a deficiency of vitamins in the mother's diet, thus depressing the mammary secretion and the endocrine system of the fœtus, in overfeeding of the child when born, and insufficient feeding of milch animals. Rao, who isolated *Bact. coli* from the liver and ascitic fluid, believed that the essential factors are cow's milk and the toxins of *Bact. coli*. In favour of this hypothesis, he found that the substitution of modern infant milk foods for cow's milk prevents the occurrence of further cases in cirrhosis families. One critical instance is cited of mixed twins in which the female on cow's milk developed cirrhosis, whilst the breast-fed male escaped.

Pathology.—Gibbons gave an elaborate and most careful account of the pathological anatomy of this disease ; he concluded that it is a peculiar form of biliary cirrhosis, the consequence of the action on the liver-cells of some irritant of gastric origin, which leads to degeneration of the cells in the first instance, with subsequent increase of intercellular connective tissue and, later, of the portal sheaths. The formation of new bile-ducts between the hepatic cells, which is a well-marked feature, he regarded as evidence of a natural curative effort, having for its object a regeneration of the liver-cells. Green-Armytage called the disease intercellular hepatic cirrhosis. R. Rao (1935) contributed the most profound

at least three months from the time of apparent recovery; light French wine may then be permitted.

Appended, as a guide for convalescent cases of sprue, is a diet table, which should be continued as long as possible.

Suggested Diet for Convalescent Cases of Sprue

Breakfast.

Well-boiled porridge (Quaker oats) or gruel. Sour milk (yoghourt).
Lightly boiled egg.
Toast, rusks or biscuits
Cocoa, weak tea,[1] or chocolate made with milk.
Butter in small quantities with toast or rusks.

1 a.m.

Warm milk or Sprulac, half a pint.

Clear liver soup, or chicken broth.
Chicken, preferably minced, boiled or roast.
Underdone minced beef.
Spinach, vegetable marrow, young peas, cauliflower, or French beans.
Milk puddings: sago, semolina.
Baked apple or banana.

Tea.

Weak tea.
Toast.
Wafers, water or Marie biscuits.
Madeira cake. Sponge fingers.

(Dinner should be the lightest meal of the day.)

Dinner (7 p.m.).

Brains.
Sweetbread.
Fruit or calves-foot jelly.
Arrowroot.

Fruits permitted.

Strawberries, commencing with ¼lb.; maximum, 3 lb.
Raspberries, blackberries (as above).
Hot-house grapes.
Fruit jellies.
Bael fruit, bananas, oranges, papaya, tomatoes.
Ripe pears.

Articles of diet to be avoided.

Salmon, trout, mackerel, herrings.
Cheese.
Fresh bread.
Jams, especially marmalade.
Grease or fat.
Suet puddings.
Nuts.
Cakes with raisins.
Baked or fried potatoes.
Pastry.
Alcoholic drinks, especially spirits, gin, brandy and whisky.
Mineral waters.

Treatment of complications.—Careful search should be made for any co-existing infection from which the patient may be suffering. Malaria, especially benign tertian, and, more important still, syphilis, may prejudice recovery. Sprue patients with syphilis tolerate antisyphilitic treatment well and their general condition is benefited. Sprue may be complicated by amœbic dysentery, and in such cases vigorous treatment with emetine and emetine-bismuth-iodine may be necessary before any improvement in the general condition is noted. Acute appendicitis quite commonly complicates sprue and may necessitate operation, with the result that the underlying sprue is improved. Sometimes acute lobar pneumonia may supervene, and it has been noted that the sprue symptoms have been much improved after recovery.

Oral sepsis.—Carious teeth and pyorrhœa must be attended to after the subsidence of acute symptoms, but care should be exercised; it is a mistake to advocate too rapid extraction, as this is apt to provoke relapse.

---

[1] Sprue tea is best made with boiling milk in place of water.

HILL DIARRHŒA

Definition.—A form of morning diarrhœa accompanied by flatulent dyspepsia and the passage of copious liquid, pale, frothy stools. It occurs principally in Europeans on visiting the hills after residing for some time in the hot lowlands of tropical countries. Hill diarrhœa is a frequent precursor of the fully developed disease—sprue.

Geographical and seasonal distribution.—Crombie, who gave an excellent account of this disease in India, pointed out that a similar affection may show itself in the highlands of Europe, Africa, and possibly South America. Steen described a similar diarrhœa in Java, where it is known as "Bandoeng sprue." There is no reason, therefore, to suppose that hill diarrhœa is peculiar to India, although, owing to the large European population frequenting the hill sanatoria in that country, it has been particularly noticed there. An elevation of 6,000 feet or over, when combined with an atmosphere saturated with water vapour, is particularly favourable to its development. In India it is found to begin and end with the rains, during which, in certain years and places, it is apt to assume almost epidemic characters. Thus, during the wet season of 1880, in Simla, an epidemic of hill diarrhœa affected from 50 to 75 per cent. of the European population, three-fourths of the cases appearing within a week of each other. In some years hill diarrhœa is less prevalent than in others; but at the proper season few of the various hill sanatoria of India are without cases.

Ætiology and pathology.—It is difficult to say what may be the precise factors determining this disease. Low barometric pressure associated with great elevation above the sea-level may be a favouring circumstance. Damp seems to be indicated by the fact that the disease occurs principally during the rains. Chill after exposure to the high temperature of the plains has possibly an important share, but hill diarrhœa is certainly something more than an intestinal catarrh. There are no adequate grounds for connecting it with either the water or the food supply, though at one time Duncan advanced the hypothesis that mica in the drinking-water caused irritation of the intestinal mucosa. There is little doubt that it is in some way connected with sprue. Steen in Java suggested suprarenal insufficiency as the primary cause, but his views have not received much support.

Symptoms.—Without very obvious cause, the patient, who in other respects may be in good health, soon after arrival at a hill sanatorium becomes subject to a daily recurring diarrhœa, the looseness coming on regularly every morning some time between 3 and 5 o'clock. The calls to stool are apt to be sudden and imperative. The motions passed are remarkably copious; very watery in some instances, pasty in others. They are pale, frothy, and like recently stirred whitewash, so devoid are they of biliary colouring matter. Their passage is attended with little or no pain, often with a sense of relief. From one to half a dozen or more such stools may be voided before 11 a.m. After that hour—at all events, in ordinary cases—the diarrhœa is in abeyance for the rest of the day, and the patient may then go about his duties or pleasures without fear of inconvenience.

The distinctive features of this form of diarrhœa are, therefore, the regularity of its recurrence every morning and its cessation after a certain hour in the forenoon; the absence of colour in the stools; and the attendant flatulence. The abdomen is sometimes blown out like a drum, the patient being conscious of unpleasant borborygmi associated with a feeling as if some boiling or chemical operation were proceeding in his inside. Occasionally the stools are very pale

although there is no diarrhœa. A certain proportion of patients in whom symptoms persist develop the clinical picture of sprue.

Treatment.—The treatment recommended by Crombie, and endorsed by other medical men of experience in India, consists of a strict milk diet, rest, warm clothing, a teaspoonful of liquor hydrargyri perchloridi in water about fifteen minutes after food, and 12 gr. of pepsin, or a corresponding quantity of lactopeptin, two hours later. If, in spite of treatment, the disease persists, the patient must return to the low country.

CHAPTER XXX

INFANTILE CIRRHOSIS OF THE LIVER

A SPECIAL type of liver cirrhosis in Indian children was first described by Sen (1887). The disease appears to be peculiar to India, though a few similar cases have been reported from Mexico and North China. Cirrhosis of the liver of unknown ætiology is widespread in young adults in the tropics, especially in the East Indies (*see* p. 31).

This disease is prevalent in Hindu children. In Calcutta, from 1891 to 1893 inclusive, infantile biliary cirrhosis—the name given to the disease—caused 1,748 deaths. Although the Hindu and Mohammedan populations of that city are about equal, as many as 1,616 of the deaths occurred in Hindus, whilst only 80 occurred among Mohammedans, the balance of the mortality being among the Eurasians and other races. The disease occurs principally in children under one year, rarely attacking those over three years. Rao (1941) stated definitely that it most commonly occurs in children between the ages of six and twenty-four months, that it is not found in Moslems or Europeans, and that it occurs chiefly in vegetarian families. As a rule, it begins during dentition, or about the seventh or eighth month, running a fatal course in from three to eight months. In rare cases it may commence within a few days of birth. Instead of lasting several months, its progress may be much more rapid, and terminate in death in from two to three weeks. In India it is common in Bengal, Madras, Bombay Presidency, and the United Provinces ; it is more prevalent in rural districts than in towns.

Ætiology.—The cause of infantile cirrhosis is unknown. Neither alcohol, syphilis, nor malaria has anything to do with it. The children of the well-to-do are relatively more frequently attacked than those of the poor. It tends to run in families, child after child of the same parents succumbing within a year or two of birth. Mukerji remarked that the disease is especially apt to occur in grossly overfed and pampered children in Bengal, and has adduced evidence that the virus is probably conveyed by the mother's milk to the child. Green-Armytage believed the true ætiology to be a deficiency of vitamins in the mother's diet, thus depressing the mammary secretion and the endocrine system of the fœtus, in overfeeding of the child when born, and insufficient feeding of milch animals. Rao, who isolated *Bact. coli* from the liver and ascitic fluid, believed that the essential factors are cow's milk and the toxins of *Bact. coli*. In favour of this hypothesis, he found that the substitution of modern infant milk foods for cow's milk prevents the occurrence of further cases in cirrhosis families. One critical instance is cited of mixed twins in which the female on cow's milk developed cirrhosis, whilst the breast-fed male escaped.

Pathology.—Gibbons gave an elaborate and most careful account of the pathological anatomy of this disease ; he concluded that it is a peculiar form of biliary cirrhosis, the consequence of the action on the liver-cells of some irritant of gastric origin, which leads to degeneration of the cells in the first instance, with subsequent increase of intercellular connective tissue and, later, of the portal sheaths. The formation of new bile-ducts between the hepatic cells, which is a well-marked feature, he regarded as evidence of a natural curative effort, having for its object a regeneration of the liver-cells. Green-Armytage called the disease intercellular hepatic cirrhosis. R. Rao (1935) contributed the most profound

study up to date by the application of the silver impregnation method. He concluded that the disease is a subacute *toxic* cirrhosis indistinguishable from Lænnec's cirrhosis. He emphasized the varying degrees of necrosis of the liver cells, the avascular œdematous connective-tissue network, and the obliterative lesions of the terminal and some of the bigger divisions of the hepatic venous tree without appreciable changes in the portal and biliary trees. There is also a poor attempt at regeneration of the hepatic parenchyma.

Symptoms.—Commencing insidiously, the characteristic initial enlargement of the liver may have made considerable progress before the disease is suspected. In the course of one or two months the liver has enlarged to the iliac crest. It is smooth and hard, and in some cases also the spleen is hypertrophied. Nausea, occasional vomiting, sallowness, feverishness, constipation, anorexia, irritability of temper, thirst, and languor call attention to the child's condition. Fever of a low type sets in; the sallowness deepens into profound jaundice; the stools are clay-coloured, the urine is dark with bile, and there may be a terminal ascites, with puffiness of the feet and hands. (Fig. 80.) The skin may be bronzed almost as deeply as in Addison's disease. In five months from the onset, ascites and œdema of hands, feet and eyelids appear, and in the terminal stages (8–10 months) gastro-intestinal hæmorrhages are found. Sooner or later, death from cholæmia ensues. The leucocyte count varies from 14,000 to 50,000 in the terminal stages, the increase being due to lymphocytes. The accompanying anæmia is microcytic.

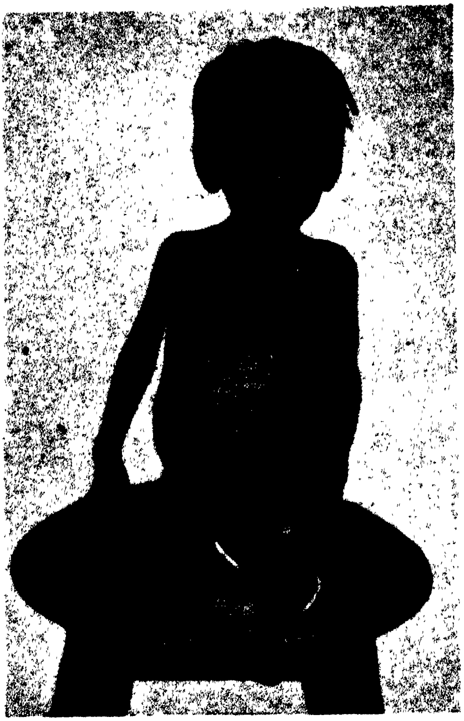


Fig. 80.—Advanced case of cirrhosis of the liver with ascites and œdema of the hands and feet, but no jaundice. (*After Rao.*)

Treatment.—According to Green-Armytage, when cases are seen early and parents are given the necessary instruction, recovery takes place in six to ten weeks. Whenever possible, in a family in which several cases of this disease have already occurred, the latest baby should be immediately removed from the mother and artificially nursed.

Prophylaxis.—The mother must be fed properly in the antenatal and nursing periods. When weaning begins, the child should be fed on specially prepared infant foods, and 2–3 oz. of fresh fruit should be given daily; iodized salt (iodosol) should be added to all food, as vegetables in Bengal are deficient in salts.

Section IV.—INFECTIVE GRANULOMATOUS DISEASES

CHAPTER XXXI

LEPROSY

Definition.—A chronic infective granulomatous disease produced by the leprosy bacillus, characterized by lesions of skin, nerves and viscera, ending in local anæsthesia, ulceration and trophic lesions. After a prolonged course it is usually fatal.

History.—The ancient history of leprosy is wrapped in the mists of time. It has been thought by some that the Egyptian records of 1350 B.C., in the reign of Rameses II, refer to this disease, although Rüffer found no evidence of leprotic mutilation in thousands of mummies he examined. In the same way, the writings of Confucius in China may possibly refer to leprosy, but is it certain that the Biblical accounts really concern the disease as we know it to-day ? When leprosy reached Greece it was first known as elephantiasis, but Aristotle in 345 B.C. clearly described its malign signs and symptoms. History relates that it was unknown in Italy until the return of Pompey's legions from the East in 62 B.C. Galen wrote of the disease in Germany in A.D. 180. Spain became contaminated by Roman troops in the fifth and sixth centuries, and by the ninth and tenth it was common in France. Thereafter, there is some mention of the disease in England, leading to the establishment of the first leper hospital in Nottingham in A.D. 625. In due course it appeared in Wales, Scotland, the Shetlands, Faroe, Iceland and Greenland but, probably, while it was most prevalent in Western Europe in the Middle Ages, it began to decline during the fourteenth and fifteenth centuries. It was endemic in Ireland up to 1775, and the last British leper died in Shetland in 1798. At present it still simmers in the Iberian Peninsula, Norway, the Baltic Provinces, Southern Russia and Turkey. With the discovery of the West Indies and the American Continent, leprosy spread to the Western Hemisphere, where it was previously unknown, and for this the nefarious influence of the slave trade must be held primarily responsible.

This sorry tale, however, pales in contrast with the rapidity of its extension in the Pacific during the latter part of the nineteenth century. Introduced by Chinese into Hawaii in 1848, it spread like wildfire. The most serious outbreak was in New Caledonia, where it was introduced in 1863, and two years later one-quarter of the population had been attacked.

Epidemiology.—Various estimates have been made of the total number of lepers in the world. From official figures, admittedly incomplete, they number about 2,500,000, but this is undoubtedly an underestimate, and the true figure is probably about four to five millions. The most striking fact brought out by Rogers and Muir, in their study of climatic factors, is that every country with a high rate of incidence (5 per mille and over) is in the tropics and possesses high annual rainfall and a considerable degree of humidity. The state of civilization and culture amongst these coloured peoples is low, and they live in small overcrowded houses under conditions of semi-civilization favourable to the spread of this disease.

The highest incidence is found in tropical Africa. The estimated rates per mille of population are 20 in Belgian Congo ; 16 in French Equatorial

Africa, and 5–10 in the British West and Central African colonies. In tropical Asia and Oceania a high rate of prevalence occurs, with rates varying from 2–22 per mille (New Caledonia and the Marquesas). In the Western Hemisphere the incidence varies from 1 in the West Indies to 3·75 in Colombia, Venezuela and Brazil. The world-wide relation between rainfall and leprosy incidence is seen in the noteworthy fact that leprosy is almost completely absent from those parts of the tropics with a rainfall of less than 10 inches per annum.

In temperate climates and in North Europe the rate appears to be nowhere over 1 per mille with the exception of parts of India, China and the Southern portion of Japan, in areas with a comparatively high rainfall. The explanation of these basic facts appears to be that dry heat is inimical to the survival of the lepra bacillus outside the human body. According to Rogers and Muir, the evidence of accumulated data favours the view that the organism generally invades the body through the skin.

Rogers has furthermore suggested that mild tuberculization of a community producing an exalted immunity to the tubercle bacillus also affords some protection to leprotic invasion, *although the reverse is certainly not the case*, as it is common knowledge that lepers often succumb to pulmonary tuberculosis.

Predisposing factors.—The most important factors influencing the prevalence of leprosy are a low stage of civilization and accompanying grave hygienic defects. This was shown by the disappearance of leprosy from amongst a number of infected Norwegian immigrants into the United States when leprosy died out as a result of the greatly improved hygienic conditions under which they lived. It has become clear, moreover, that there is little or no tendency in leprosy to spread at the present day under favourable hygienic conditions in temperate climates. Defective housing and overcrowding furnish favourable conditions for its spread, and in the main endemic areas the poorer inhabitants live in close proximity to one another. One fact that has been brought out strongly in the Hawaii reports is the effect of irregular sexual relationship with native women, and in the Marquesas Islands epidemic leprosy was spread by the prevailing promiscuity. Sociability, too, has been found to favour its spread ; thus, in Norway Hansen recorded that formerly it was considered impolite to refuse to sleep in the same bed as a leper, if he was not in an advanced and noticeable stage of the disease. The habit so prevalent in the Pacific Islands of smoking communal pipes and of eating out of the same dish naturally also favours infection. Absence of fear of the disease, as in native tribes of Central Africa and in the Pacific, and their objection to isolation of lepers naturally encourage direct contagion.

Diet is said to predispose to leprotic infection, especially the edible yam root—colocasia—in the Pacific Islands.

Epidemic diseases, such as typhus or plague, attended by a high general mortality, have in the past resulted in great, though temporary, decrease in prevalence of leprosy.

Ætiology.—The universal and ancient conviction of the infectious nature of leprosy is accepted everywhere, but during the nineteenth century there existed a deep-rooted belief in the almost exclusive origin of leprosy through heredity. Native belief for centuries in China, Japan and Central Africa has been moulded on the heredity theory, but it was held that this taint does not make its appearance until puberty.

In St. Kitts Munro found, in 64 cases with reliable family records, that there was no family history in 34, whilst of the remainder there existed a direct history in 9 only. During the past decades much positive evidence has been obtained against the heredity theory. First, there is the diminished fecundity of lepers, which is well known. The rapid increase of leprosy in Hawaii could by no means be explained on any hereditary basis. The most striking example, however, in history is the observations of Hansen on 170 Norwegians who migrated to Minnesota, U.S.A. when suffering from the disease; not one of their descendants, up to the third generation, had contracted leprosy in America.

Contagion.—It is generally accepted that leprosy is conveyed from the sick to the healthy by contagion, and this is emphasized by all who have written on this subject, such as Brousse in Trinidad (1879), Hills in British Guiana (1881), and Leloir in the Hawaii reports of 1886. A native of a non-leper colony may acquire the disease on visiting a leper country and, moreover, may communicate it to his fellow countrymen on his return. One well-authenticated instance occurred in 1872 when an Irishman, who became a leper in the West Indies, returned and conveyed it to his brother in Dublin. The Editor studied a somewhat similar case in a woman whose husband—a Mauritian—had died of leprosy, and who developed the disease in London, where she had lived all her life, after an incubation period of seven years.

Intimate contact appears to be necessary, combined with lowered resistance and susceptibility to infection, because implantation of the bacillus does not alone suffice. Many attempts have been made in the past to communicate leprosy to man by inoculation; all, with two questionable exceptions, have failed. De Langen (1936), however, reported the case of a European in Java who was injected with morphia from a syringe previously used on a leper; six months later a leprous nodule appeared on the forearm at the exact site of the morphia injection; subsequently, lepromatous manifestations were noted. In June, 1936, Lagoudaky was twice inoculated intramuscularly with leper blood. Some forty-four days later two small subcutaneous leprous lesions appeared and he was demonstrated in 1938 at the International Leprosy Congress.

The rapid spread of leprosy in a susceptible community is difficult to reconcile with the statement that in many instances contact under favourable circumstances has failed to convey the disease. Thus, in those who have lived for a long time in attendance on lepers there have been only a very few instances of infection, e.g. the historic cases of Father Damien at Molokai, and two Sisters of Mercy and the Medical Superintendent at Robben Island in South Africa. But hundreds of attendants on lepers pursue their work for years unscathed. In Louisiana 19 Sisters of Charity have been in attendance on lepers for 41 years without one single instance of infection.

As with tuberculosis, evidence points to the susceptibility in early life.

The relationships involving intimate contact in childhood are most important. This has been realized in the Culion Island leper colony (Philippines) where children of lepers removed from their leprous surroundings do not contract leprosy. Amongst 10,000 lepers there Denny noted that 35 per cent. were brothers and sisters, 27 per cent. cousins, 11 per cent. children of lepers, 7 per cent. parents of lepers but only 1 per cent. husband and wife. In Japan it is recorded that 7 per cent. of children of lepers contract the disease.

Bacillus lepræ (*Mycobacterium lepræ*).—This organism is the accepted cause of leprosy and is present usually in great profusion in the tissues. In size, shape and staining reactions it closely resembles the tubercle bacillus. It exhibits marked pleomorphism; the ends are somewhat attenuated and by some it is said to possess a gelatinous capsule. Individual bacilli vary in size, from 1·5 to 5 μ in length and from 0·2 to 0·5 μ in breadth. Curved forms with pointed ends are not uncommon. In the reactionary stages of the disease the organisms may be granular, coccoid, mono- or bipolar. Round, spore-like bodies often impart a granular appearance to a clump of bacilli. In common with the tubercle and smegma bacilli *Myco. lepræ* is acid-fast, retaining carbol fuchsin stain after being treated with mineral acids, though it may be distinguished from *Myco. tuberculosis* by being more easily decolorized by alcohol than by weak acids. Moreover, it occurs in large numbers in the lesions, chiefly in zooglœa masses within the lepra cells, often grouped together like bundles

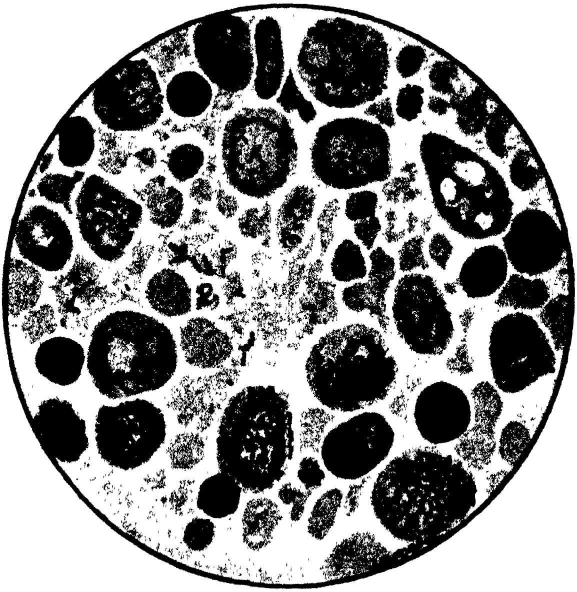


Fig. 81.—Section of spleen showing lepra cells and lepra bacilli. × 800.

of cigars or arranged in a palisade. Chains are never seen. Most striking are the intracellular and extracellular masses, known as *globi*, which consist of clumps of bacilli in capsular material. (Fig. 81.)

The bacilli can be readily demonstrated by excision of a leproma, or they can be obtained by clamping a nodule, pricking the solid tumour, collecting a droplet of expressed " leper juice " on a coverslip and staining by the Ziehl-Neelsen method. They are Gram-positive. They are found in all primary deposits, in the skin lepromata, in marginal infiltration of the macular eruptions (where they may be very sparse), in apparently normal skin in the vicinity of leprous lesions, in the early stages of leprous neuritis (where also they may be present in small numbers) and in the specific lesions in the liver, spleen, testes and lymphatic glands. In the blood vessels they have been found in the endothelium and occasionally free in the blood, or engulfed by leucocytes. This fact is specially useful in diagnosis when thick dehæmoglobinized blood-films are stained by Zeehl-Neelsen stain. Bacilli are also abundant in the purulent and mucoid discharges from the nose, as well as from ulcerating lepromata. Very rarely have they been found in the spinal cord or lungs.

Cultivation of *Myco. lepræ*, though repeatedly attempted, has never been really successful. Some investigators, it is true, have obtained growths of acid-fast bacilli (chromogenic and non-chromogenic), or diphtheroids, which in some instances have developed acid-fast forms on subculture. Others have described branching bacilli, granular and coccoid forms.

It is probable that all four varieties (diphtheroid, pigmented acid-fast, apigmented acid-fast and acid-fast streptothrices) have been more or less commonly encountered in leprous tissue in various parts of the world. When some of these cultures are injected transient granulomatous lesions have been obtained, but there is general agreement that they do not constitute true leprotic lesions.

Inoculation of animals with human leprous material containing prodigious numbers of organisms does not give rise to typical progressive leprous lesions. Adler (1937) succeeded, to a limited extent, in communicating leprosy to young splenectomized Syrian hamsters (*Cricetus auratus*). A fragment of lepra nodule was inserted under the skin and, when the animal was later killed, leprosy bacilli were demonstrated in the liver, and (in other animals) in neighbouring enlarged and caseating glands, but he failed entirely to carry on the disease by subinoculation in a continuous series of hamsters. Similar results have been obtained by Burnet. Subsequently Dharmendra and Lowe in India, in a series of carefully planned experiments on the same animals, by implantation into the abdominal wall and intraperitoneal inoculation, failed to produce generalized or progressive infection. When the nodule was implanted into the abdominal wall, masses of bacilli were found at the site of the implant, but not beyond, and bacilli were found elsewhere in two animals only. The fact seems to be that lepra bacilli can survive for long periods in inoculated animals and even dead bacilli may evoke local reactions and produce pathological appearances similar to those produced by living organisms. Araujo in Brazil appears to have had experiences similar to those of Adler and to have found the organisms in the European hamster (*Cricetus cricetus*) in great profusion. Collier (1940) implanted lepromatous material beneath the skin of monkeys fed on a diet of *Colocasia* (Yam) over a long period. It is claimed that some developed symptoms reminiscent of leprosy in man and that acid-fast bacilli were obtained from material procured from the ears of these animals.

Rat leprosy.—A leprotic disease of the rat, which occurs naturally throughout the world, was first observed by Stéfansky in Odessa in 1903. Two types are recognized: disease of skin and muscle and disease of lymphatic glands. In tropical rats it occurs commonly and has been specially studied by Lampe and de Moor in Java. House rats are usually affected, especially *R. rattus concolor* and *R. decumanus*. Infection in these animals is conveyed by injury and by cannibalism. Laidlaw succeeded in transmitting this disease to the Syrian hamster, and it can also be conveyed to rats of the same species, infection taking place readily through skin abrasions and subcutaneous inoculation. The bacillus is *Mycobacterium lepræ murium*, morphologically indistinguishable from *Myco. lepræ*, whilst the lesions resemble those of human leprosy, macroscopically as well as histologically. Attempts at cultivation have shown much the same negative results as in human *Myco. lepræ*.

In spite of the general similarity of human and rat leprosy, it is generally agreed that the organisms represent two separate and distinct species and there does not seem to be any connection between this disease of the rat and human leprosy.

Pathology.—*Spread of leprosy through the body.*—*Myco. lepræ* enters the skin either by direct inoculation, or by spread from another focus, possibly carried by wandering cells. Passing through the capillary walls, the bacilli lie in the perivascular lymphatics or are ingested by endothelial cells and histiocytes. The process is difficult to follow in the case of macules with scanty bacilli, which spread centrifugally. The bacilli pass from the cutis to the main nerve trunks by the lymphatic channels and are found lying singly or in groups between the nerve fibres. Metastatic spread through the bloodstream and auto-inoculation through abrasions also occur. Bacilli have been found in the corium of the skin over almost the whole body. It was formerly supposed that they were absent from the soles of the feet and palms of the hands, but this is incorrect; macroscopically, the lesions are inconspicuous in these situations owing to cornification of the skin.

In advanced lepers the mucous membrane of the nose, mouth and pharynx are affected, and the eye frequently, both superficially and deep. The lungs, even in the most advanced stages, escape to a great extent. The liver is usually invaded, and bacilli are found in the interlobular connective tissue and around the central veins. The interstitial Kupffer cells are swollen with bacilli, which, however, do not penetrate the parenchyma cells.

In acute advanced cases the spleen is often involved, especially in the arterial sheaths and the Malpighian bodies. The glands at the hilum are frequently infiltrated. Small numbers of bacilli have been demonstrated in the œsophagus, stomach and intestine, with involvement of corresponding lymph glands. Absence of intestinal ulceration characterizes leprosy. In nodular leprosy the bacilli may be present in the glomerulus of the kidney, when they may cause hyaline degeneration and interstitial nephritis; which is quite common in leprosy.

In a large proportion of cases of nodular leprosy of prolonged duration albuminoid or lardaceous disease of the alimentary canal, liver, spleen and kidneys ensues.

The suprarenals are attacked in all cases in which the liver and spleen are affected. The testicles are to a great extent destroyed in all nodular cases by inter- and intra-tubular invasion. The testicular tissue is finally completely destroyed.

Leprous affection of lymphatic glands is histologically obvious. The glands are swollen, but without alteration of form. On section, the ampullæ and medullary cords are yellow, or yellowish-brown, which renders them unmistakable. The inguinal glands are especially affected and the lower members of the group may be as large as pigeon's eggs. Microscopically, the ampullæ and trabeculæ are filled with *globi*: evidently lymph cells which have become filled with bacilli. The circulation through the glands is not arrested; nevertheless, they retain their infectious products. Suppurating lymph glands are, not infrequently found in skin leprosy, especially in the groin and neck. On the other hand, especially in the Pacific Islands, these glands may be tuberculous, or may even contain both leprosy and tubercle bacilli.

Distribution of bacilli in skin and nerves.—In the skin the leprosy bacilli may be destroyed by the tissues of the body; they may be latent, or they may multiply and spread. The vessels of the corium are arranged in two plexuses: the superficial or subpapillary and the deep or subcutaneous. These communicate through vessels adjacent to the hair-follicles and sweat glands. The subpapillary plexus supplies branches to the papillæ; the deep communicates with arterial and venous vessels lying in the subcutaneous tissues. Nerve-plexuses correspond to those of the vascular system.

The spread of leprous infection in the corium takes place in the lymphatic channels. In some lesions the superficial plexus and its papillary branches are involved, in others the whole thickness of the corium. In others again spread is primarily along the deep plexus, invasion of the superficial layers taking place along the hair follicles, resulting in the pebbly appearance of some tuberculoid leprosies.

The central nervous system is seldom the site of leprous lesions. When secondary degeneration of the spinal tracts takes place it is due to extreme destruction of peripheral nerves, but the spinal and Gasserian ganglia have been found to contain bacilli. Septic abscesses of the larger nerve trunks, especially the ulnar, are sometimes found.

Wherever leprotic infection advances there is a general or local reaction on the part of the tissues to arrest the invasion. In the lepromatous type this reaction is generally limited, but in the neural it may be pronounced, and the leprotic process may remain for years confined to a single lesion.

Lepromatous (nodular) leprosy.—Young lepromata present a smooth, white, glistening appearance on section, but the older appear browner. The specific lesions of leprosy differ from that of tuberculosis, inasmuch as they are well supplied with blood vessels and never undergo caseation. The earliest recognizable lesions are generally multiple, the result of bacillary metastasis from some unknown reservoir. The more acute the process, the more numerous the foci. Lesions are classifiable as nodules, papules, macules and diffuse infiltration.

Nodules, round elevations of skin of limited size, may be temporary or permanent, soft vascular or fibrous. The nodule is probably formed at the site of a bacillary embolus, either in normal skin or in a portion already infiltrated with leproma. (Figs. 82, 83.)

Papules are smaller than nodules, not larger than a split pea.

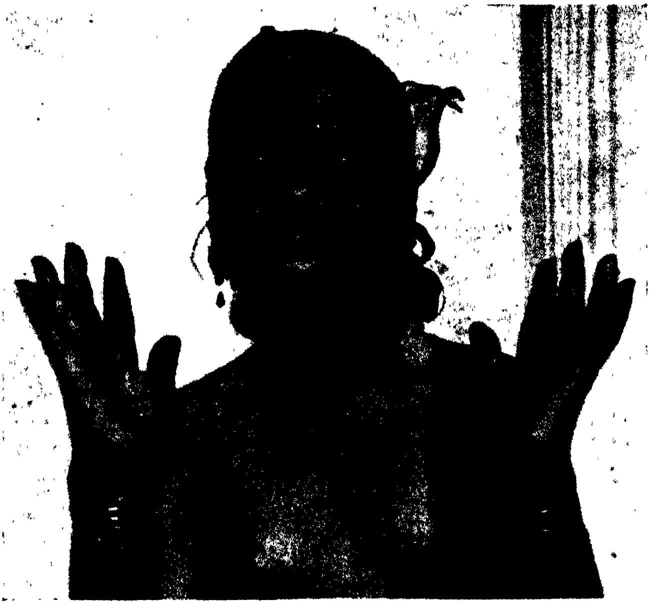


Fig. 82.—Egyptian child, aged 11, showing acute early nodular leprosy. (*Dr. H. K. Giffen.*)

Macules are roughly circular or elliptical patches of discoloured skin, and are found in both the main types of the disease.

Diffuse infiltration of the skin is often noted without the appearance of nodules or macules. It is due to infection of the skin at numerous points accompanied by cellular infiltration, but response to the invading bacilli is insufficient to produce clinically noticeable signs. In resolving lesions the skin may assume a thin atrophic appearance resembling crushed parchment.

The essential cell in defence against leprosy is the macrophage (histiocyte).

There seems to be an allergic element in tissue response in leprosy. The early reaction to *lepromin* is probably allergic, but it is not clear that the late, true reaction is the same. The lepromin test is usually negative in lepromatous cases, positive in tuberculoid and nervous cases, and usually positive in child contacts, especially in the later years of childhood.

When the resistance of the individual is high, characteristic histological changes are: concentration of round cells, especially round hair follicles and vessels and development of the "tuberculoid focus," similar to tuberculosis. The essentials in the histology of the skin in resistant or neural leprosy are: localization of the process in the skin, the foci being chiefly perifollicular and perivascular; formation of epithelioid and giant cells; invasion of the subcutaneous nerves.

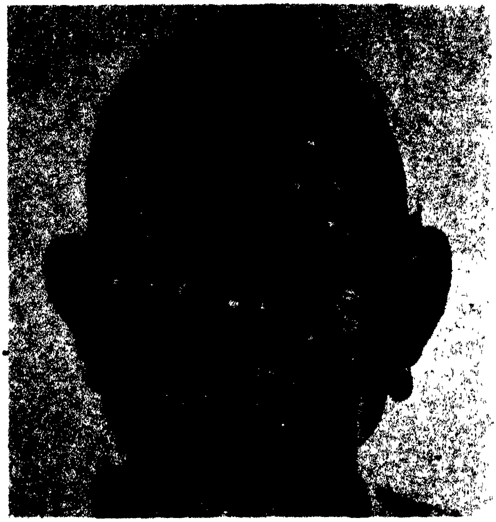


Fig. 83.—Nodular leprosy in an Egyptian.
(Photo, Dr. H. K. Giffen.)

The histopathology of the nerve lesion corresponds to that of the skin. In advanced lepromata bacilli and lepra cells are more abundant and there is formation of fine fibrous tissue in the endoneurium which may later contract and block the nerve-fibres. In the neural type bacilli are few, though it is easier to find them in nerves than in the skin. The cellular reaction also tends to be more intense so that epithelioid and giant cells are present in greater or lesser numbers surrounded by small round cells. Thickened nerve trunks may become enclosed in a dense fibrous sheath which may later cause constriction.

In the non-resistant case the essential cell is the macrophage but, as the bacilli multiply, so no attempt is made to localize infection, owing to the relatively lowered resistance of the tissues. The bacilli multiply rapidly, the macrophages become active and phagocytose the bacilli. These are the "lepra cells" which are uniformly distributed beneath the epidermis (see Fig. 81, p. 556).

In lepromatous leprosy there is no centralization of " lepra cells " in the granuloma ; nerves in the cutis stand out and do not appear to be invaded. As this process continues, the invasion of the cutis becomes more intense, and all the skin elements become involved and eventually unrecognizable, so that the epidermis becomes flattened, and the whole subcutaneous tissue, including the subcutaneous fat, is invaded by the granuloma. The lepra cells now appear to give up the attempt at phagocytosing the bacilli and undergo a curious foamy degeneration (foamy cell of Virchow). There is marked absence of gross invasion by lymphocytes. Owing to the ease with which the bacilli multiply they are carried by the lymphatics throughout the body and there is general dissemination and multiplication, especially in the reticulo-endothelial system (Fig. 84.)

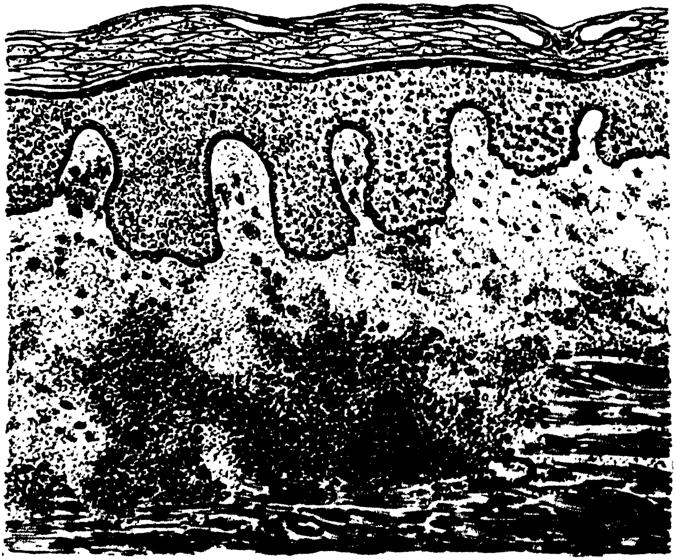


Fig. 84.—Early lepromatous lesion, showing diffuse infiltration of sub-papillary, and dense infiltration of sub-epidermal layers.

Tuberculoid lesions.—The epithelioid cell is distinctive of the tuberculoid lesion, not only in the skin, but also in the nerves ; it seldom, if ever, contains lepra bacilli. Indeed, it is usually difficult, or quite impossible, to find bacilli in this type of lesion. The so-called " giant cell of Langhan's " is another characteristic, and occasionally a few bacilli are found in connection with it. This cell may be of considerable size and is found in skin and nerve tissue surrounded by numbers of small lymphocytes. In typical tuberculoids the cellular elements are arranged in dense cords, which in section resemble tubercles (Fig. 85).

The activity of lesions is indicated by abundance of typical epithelioid cells, and in major tuberculoid the inflammatory process may be so acute that necrosis and ulceration of the skin take place.

Immunity.—Contrary to the popular belief, there seems little doubt that there is a natural immunity to infection which varies in degree in different individuals. Susceptibility to infection may depend upon general health, because it is certain that debility from any cause lowers resistance to leprosy. Varying individual resistance is also exemplified by the type of the disease. The nerve type, with tuberculoid lesions and few bacilli, indicates a comparatively high resistance and the multibacillary lepromatous form a comparatively low resistance. In the former, Mitsuda's skin (lepromin) test is usually strongly positive, in the latter negative.

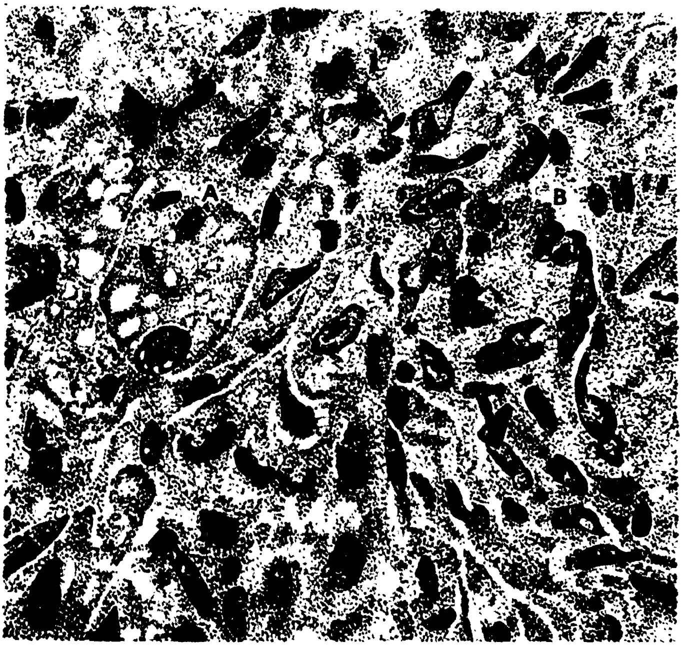


Fig. 85.—Early lepromatous lesion, showing large foamy cell (A) in the deeper tissues and a leprotic giant cell (B). The main cells are epithelioid in type. (*After Cochrane.*)

The suggestion has been made that this test may be employed in non-leprous subjects as an index to resistance to leprosy. Applying it to non-leprous children of leper parents, Rotberg found that positives increased with increasing age, reaching the maximum of 50 per cent. at the age of ten. This is taken to indicate that resistance is low in young children, but increases with age, but there is no evidence, as in tuberculosis, that resistance may be ultimately broken down by massive or repeated infections, whilst slight infective doses tend to raise resistance. Another indication of resistance is the abortive case, when slight, though definite, lesions appear and disappear without apparent cause. About the inheritance of acquired immunity there is still little clear knowledge.

In Burma leprosy is of a much more severe type in native Burmese than in Indians living in that country. Some authorities have claimed that racial immunity is the result of prolonged and intimate contact with leprosy at some remote period of history and its disappearance as an endemic disease has been explained on this basis, but there is really little evidence to support this. It is more natural to explain the persistence of endemic leprosy in certain European countries, and its disappearance from others, on the basis of improved sanitation and hygiene than on racial immunity.

Localized immunity is observed in active lesions, especially those of the tuberculoid type. In the annular form of eruption the active inflammation spreads at the margins while the disease dies down at the centre, leaving only a slight discoloration or perhaps a mild sensory impairment; or, again, a major tuberculoid lesion may flare up and die down again, leaving only a slight visible scar to indicate its former site.

Probably the majority of humans are non-susceptible to leprosy save during the critical years of childhood and adolescence. Even when infection does take place there is a natural tendency to recover, so that the possibility of arrest in the initial stages has only been realized in recent years. Cochrane has shown that in children more than 50 per cent. of all neural lesions show improvement over a period of three years; possibly this is related to the lepromin reaction, as the great majority give a positive result.

Clinical features.—*Primary infection.*—The early manifestations of leprosy may be vague and indefinite, such as malaise, weariness and mental depression. The probability is that bacilli reach the corium of the skin, or mucosa of the nose, mouth or pharynx, through some breach of the epithelium. It is difficult to be certain whether the primary lesion is the initial one, or some metastatic manifestation but, when several appear on widely-separated parts of the body at the same time, they naturally represent secondary lesions derived from some primary focus. Rogers stressed the following points as worthy of notice. In hilly and stony districts in India the primary lesions are most commonly observed on the feet. No lesions of the scalp are recorded. The first lesions on the body are scattered most densely on the extensor surfaces, especially on those parts exposed to pressure when lying down, such as the cheeks, outer surfaces of the shoulders, arms, buttocks and outer surfaces of the thigh. The flexor surfaces, on the other hand, are remarkably exempt. The affected parts are just those most exposed to insect bites and to the excoriation by the nails in attempt to allay irritation.

The fact that leprosy is more prevalent in hot, moist climates may to some extent be explained by the greater softness and moisture of the skin and the frequency of prickly heat. In cold climates, when the body is protected by clothes, it appears that a larger proportion are inoculated through the nasal mucosa. The face around the nose is a frequent site of *leprides* which are devoid of lepra bacilli; the nasal mucosa is frequently involved and is probably the immediate site from which the leprides arise.

Incubation period.—This is undoubtedly very variable and may be very prolonged: as long as 6 to 8 years. In South Africa the average period in nodular cases is about 2 years though it would be fair to state that the general average is 3¼ years, the extremes lying between 5½ months and 4 years. It may well be that very long incubation periods may represent long latent periods after infection and before outward visible signs become apparent. Early discoloured anæsthetic patches may be overlooked for years.

In children of lepers living with their parents in the Culion Island colony in the Philippines it was observed that the disease developed in 22 children within 4 months to 4 years from the time of their removal from the source of infection. Certainly in one case it took place during the first year of life. Muir has recorded a case in a three months' old child. There appears to be direct relationship between closeness of contact with the diseased and the early development of symptoms. The length of incubation is considerably affected by the general health and habits of the patient, as well as by the climate. The first signs of leprosy may appear during the course of some other disease, such as dysentery, enteric fever, malaria or influenza.

As compared with tuberculosis, one of the chief characteristics of leprosy is the absence of toxicity; enormous numbers of bacilli may be present in the body with few signs. The local inflammatory reactions to lepra bacilli vary within wide limits. Thus, in one patient the disease is so localized that it affects one small skin area or the main nerve supply. There may be acute inflammatory swelling, local pain, trophic, sensory and other disturbances. Bacilli can be demonstrated with great difficulty. In contrast, a second case may show involvement almost of the whole body, so that a preparation taken from any part of the skin may reveal numerous bacilli though the patient is not acutely ill, and is able to be about and do his work. The nerves are not noticeably thickened, and superficially the skin appears normal. At any stage during invasion sudden exanthematous reactions may appear, accompanied by fever and general symptoms.

The *chronic onset* is so gradual and insidious that the disease has advanced to a considerable extent before any abnormality is evident. There may be tenderness, tingling or thickening of a nerve, an area of anæsthesia, perhaps with some change in the appearance of the skin, insensitiveness to burning, formication, tingling or numbness of extremities. Discoloured skin patches may be mistaken for eczema or ringworm; these may at first be small, gradually increasing in size.

In the *acute onset* there are occasionally multiple lesions with less diffused margins, which tend to spread rapidly and which contain very numerous bacilli. The first noticeable sign may be an evanescent rash. The onset may be determined by some other acute disease, such as malaria or typhoid, which lowers the resistance. It may also be the sequel to chronic infection, such as syphilis, ancylostomiasis or chronic disease of the gastro-intestinal tract. The period of life may also have some bearing, *e.g.* extra strain imposed on the body during puberty, parturition and menopause.

The clinical types of leprosy.—Though leprosy affects the whole system, its lesions are more manifest and conspicuous (1) in connection with skin and mucous membranes and (2) in the peripheral nerves. In the more acute forms, with low resistance and prodigious multiplication of bacilli, the clinical signs are mainly connected with the formation of the "leproma"—a granulation with lepra cells. In textbooks of general medicine this form is referred as to "*nodular*" leprosy. The second main type is known as *neural* and is chiefly characterized by polyneuritis and macules. It is usually more chronic and benign and is associated with greater resistance. In this form *Myco. lepræ* is difficult or impossible to demonstrate in the skin lesions. According to the recommendations of the International Leprosy Congress in Cairo (1938) the following subdivisions are recognized :—

1. *Lepromatous* 1 (*L*.1).—(Nodular).—Slight lepromata consisting of one or a few macular areas or a few small infiltrated patches, small nodules, or diffuse lepromatous changes ; no lesions of nasal mucosa.

2. *Lepromatous* 2 (*L*.2).—Moderately advanced cases with numerous macular areas or fairly numerous small or larger infiltrations or nodules. Lesions of nasal mucosa frequently present.

3. *Lepromatous* 3 (*L*.3).—Advanced lepromatous (nodular). Cases with numerous, extensive, or very marked lepromatous lesions, which vary in their stage of development or retrogression. Lesions of nasal mucosa invariably present.

4. *Neural* 1 (*N*.1).—
   - (*a*) Cases with from one to several small macules, or a smaller number of larger ones (flat or elevated), without indications of polyneuritic changes.
   - (*b*) Cases presenting only polyneuritic changes of slight degree with minor trophic disturbance.
   - (*c*) Cases showing combinations of macular and polyneuritic manifestations.

5. *Neural* 2 (*N*.2).—
   - (*a*) Cases with fairly numerous or large macules without evidence of polyneuritic changes.
   - (*b*) Cases presenting only polyneuritic changes of moderate degree and peripheral anæsthesia of considerable extent.
   - (*c*) Cases showing combinations of equivalent total degree.

6. *Neural* 3 (*N*.3).—
   - (*a*) Cases with numerous and extensive macular lesions with polyneuritic changes.
   - (*b*) Cases with polyneuritic changes, such as extensive peripheral anæsthesia, marked motor and trophic disturbances, ulcers and mutilations.
   - (*c*) Cases showing combinations of equivalent total degree.

Whilst this classification aims at describing the two main types, it is common to find both present at the same time. The case is then known as "mixed." The degree of advancement of each type is indicated by symbols, for instance, L_3—N_2. L_1—N_3.

Relative frequency of the types.—In India and Africa and also apparently elsewhere, the neural type preponderates, forming 55 to 90 per cent. of the total.

Polyneuritic lesions.—Involvement of peripheral nerve trunks produces sensory changes in the extremities, which commence distally and spread in a proximal direction. They result in trophic changes, such as anidrosis, glossy skin, keratosis, perforating ulcers, atrophy, necrosis of bones and mutilations of the extremities.

Lesions of peripheral nerves.—Thickening of nerve trunks is related to mechanical injuries. The ulnar nerve is commonly affected at the elbow, while the radial is well protected. Thickening of the branches is generally correlated with leprides of the neural type.

Leprous nerve abscess is not uncommon in India associated with the neural type, or with injury. It occurs in superficial nerves—usually the ulnar, median cutaneous of forearm, great auricular or crural. The abscess is usually central and spindle-shaped and contains pus similar to that of glandular tuberculosis. Lepra bacilli may be present.

Leprides is the term applied to macules of the neural type and polyneuritic lesions caused by involvement of large nerves. They assume the form of minor tuberculoid or major tuberculoid macules and are characteristic.

Anidrosis, preceded by hyperidrosis, may be one of the first noticeable signs.

Hypopigmentation, usually noticed in highly pigmented skins, is not usually complete, as in leucoderma, but partial.

Hyperæsthesia, with an area of the lesion tender to touch and painful stimuli, precedes anæsthesia.

Anæsthesia. At first it consists of loss of epicritic and then of protopathic sensibility.

Parakeratosis is recognized clinically by changes in the horny layer of the skin which becomes shiny and scaly.

Hyperkeratosis is best seen on the palms of the hands, or soles of the feet, and in the latter situation perforating ulcers usually form.

Hair and nails.—The hair follicles are affected ; the hairs become soft and thick, breaking off at their point of emergence. The broken end becomes club-shaped, but growth continues inside. Similar changes take place in the nails, which become thickened and curved and claw-shaped.

Vascular changes produce congestion and erythema, usually surrounding the margins of the lesion.

Resistance is the determining factor whether the type becomes neural or lepromatous ; the latter invariably shows greater concentration of bacilli in both nerves and skin. The lepromatous lesions are in the main symmetrical. Leprides and anæsthetic patches of the neural type are less so. When they cover large areas it is the result of gradually extending lesions from comparatively small foci.

The "lepra" reaction is acute in onset and course, accompanied by severe, febrile constitutional symptoms when all the lesions suddenly become swollen and inflamed. At the same time fresh nodules or macules, surrounded by œdema, appear, and cutaneous or subcutaneous nodules become pustular, break down and discharge pus full of *Myco. lepræ*, many of which are diphtheroid in shape and staining reactons. As the reaction subsides, the lesions remain covered with desquamating epithelium. This reaction may last a few days, or may be prolonged for weeks or months.

It may remain confined to the face or extend to the whole of the body. The factors which determine its onset are not so easily ascertained.

Intercurrent disease, such as malaria, may light up the lepra reaction and, moreover, in the lepromatous form, small doses of potassium iodide may produce a similar condition, but these symptoms usually rapidly fade with elimination of the drug from the body. In India there seems to be a predisposition to the lepra reaction, which is much less common in Central Africa. In the neural type the reaction differs, as the tuberculoid form of lesion is more limited so the febrile and toxic symptoms are less severe.

In both the main forms of leprosy the reaction represents an attempt to destroy the causative bacilli. In the minor tuberculoid form this is often successful when bacilli are scanty, but in the major tuberculoid, where they are more numerous, it is not. In the lepromatous form the reaction is less severe when there are masses of bacilli to be destroyed and so, as the result of toxic absorption, the patient's resistance is reduced and the lesions become even more widespread than before.

The process spreads to the nerve-trunks and ramifications. The nerves become swollen, congested and tender, and there are neuralgic pains. Blisters and bullæ may be formed, with ultimate sloughing, which may even proceed to bone necrosis. Perforating ulcers in the feet are frequently the result of nerve reaction in the lower limbs. Herpes zoster may accompany involvement of the intercostal nerves.

Distribution of leprous lesions.—Those parts of the body most exposed appear to suffer early. In Europeans these are the hands and face. In natives exposed to injury the feet are most liable.

Head and neck.—The ears are more constantly affected than any other part, and in a suspected case it is always as well to look first at the auricles, where any thickening of the lobule may be readily detected by palpation with finger and thumb. Nodular lesions are seldom seen on the palms of the hands or soles of the feet and are exceptional on the penis and scrotum. The scalp was formerly said to be seldom affected ; this is partly due to its anatomical structure, and partly to the fact that it is hidden by hair but, as a matter of fact, leprous alopecia is by no means uncommon. In the neck the cutaneous branches of the nerves are early involved, especially the great auricular, which may stand out on the skin and be quite conspicuous. Palpation of this nerve may be a great help in early diagnosis.

Initial lesions of all types are common on the face, especially on the forehead. There is often loss of hair of the eyebrows, especially the outer part, and of eyelashes, even in the early stage of the disease. Lesions of the nasal mucosa are often present, though they may pass unnoticed unless specially sought. They may cause nasal catarrh and often intermittent epistaxis. There may be merely a diffuse erythema, or erythematous patches, or general infiltration leading to corrugation of the skin. Nodular eruptions appear on the eyebrows, leading to leontiasis, and there is often a characteristic thickening of the nose. In the neural form anæsthetic patches appear, together with paresis or paralysis of groups of muscles, which create a peculiar mask-like expression (Fig. 86). When the orbicularis palpebrarum is affected the results are serious, as failure to close the eyes involves trauma of the cornea. Paresis of the sphincter muscles of the mouth leads to dribbling. The senses of taste and smell may either be much diminished or lost entirely. Pressure on the facial nerve frequently causes intractable facial paralysis.

Lesions of the eyeball may be divided into two categories : those due to the presence of *Myco. lepræ* in the eye, or those due to interference with the nerve supply.

When *Myco. lepræ* are present in the eye, lesions are caused by spread either along the lymphatics or bloodstream. It is not uncommon for the disease to spread from the face to the conjunctiva, which becomes injected and thickened. When diffuse, this process may at first resemble ordinary conjunctivitis. Later, nodules appear, which may be mistaken for pterygium. The disease may attack the cornea, which is the most vulnerable tissue ; then a ground-glass pannus spreads inwards over the pupil from the corneal margin and may considerably interfere with vision. Leprotic nodules of the cornea are by no means uncommon and, when deeper, may bulge into the anterior chamber. Again, leprotic infiltration may spread from the sclera along the anterior ciliary vessels, setting up iridocyclitis resembling that of syphilis. When there are nodules of the iris the eye

Fig. 86.—Leprotic infiltration causing paresis of facial muscles and paralysis of orbicularis palpebrarum.

is doomed. The eye may also be affected by blood-borne infection, when isolated nodules may appear on the cornea or in the vitreous, but it is rare for the retina or optic nerve to be affected when other portions of the eye remain exempt. In Rogers's experience in India, from 5–10 per cent. of lepromatous cases develop disease of the eye or its adnexa.

In the neural type the eye is often involved in an area of widespread tuberculoid or lepride. Healing is followed by sclerosing fibrous tissue. Anæsthesia of the cornea and the deposition of fibrous laminæ, together with paralysis of the palpebral muscles, abolish the corneal reflex and prevent normal closing of the eye by day or night, so that progressive ulceration of the cornea takes place, and general panophthalmitis may occur. Ectropion leads to eversion of the punctum lachrymale and discharge of tears, with eventual destruction of the lachrymal sac.

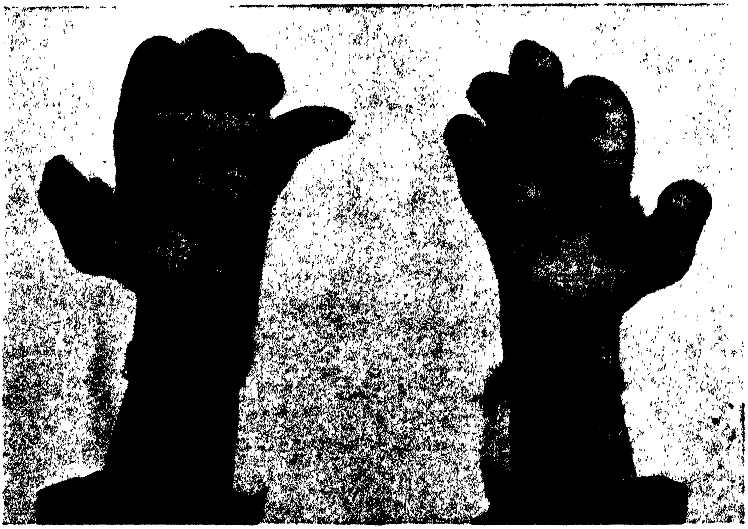


Fig. 87.—Nerve leprosy : main-en-griffe. (*Dr. H. K. Giffen.*)

The nose.—The habit of "picking" the nose, especially in children, probably plays a part in lesions of the mucosa, and those parts of the nasal septum and inferior turbinates within reach of the fingers are most commonly affected. All degrees and types of infection which occur in the skin are found in the nasal mucosa ; nodules may be present on the turbinates, ulcers and scars on the septum. Perforation of the septum and deformity of the nose may result. When there is ulceration, the discharge contains large numbers of *Myco. lepræ*, so that these cases constitute a serious source of infection to others.

Mouth, pharynx and air passages.—Lesions of the lips are sometimes found as an extension from the face. Nodules appear at the outer margins of the lips, and fibrous constriction may cause partial stenosis. Nodules of the tongue are seen in advanced cases. The palate may be affected by diffuse or nodular lesions. Perforation of the palate may occur in the absence of syphilis. The larynx is not primarily affected, but may be involved by extension ; the onset is usually insidious. In some lepromatous leprosy the soft palate, uvula and ary-epiglottic folds are swollen and indurated ; tubercles of various sizes may appear. Later there is ulceration ; constriction of the glottis may necessitate tracheotomy. Fibrous constriction is the cause of the hard whispering voice of the confirmed leper, giving rise to the brassy leprous cough. In primary nerve leprosy the throat is seldom affected. Lesions of the pharynx and tongue are exaggerated during the reactionary phase.

Upper extremities.—Primary lesions are not uncommon; in those who wear European dress they tend to be limited to the hands. The flexor surfaces tend to be much less affected than the extensor, possibly because they are more liable to injury.

Skin and nails.—The nails are not usually affected in the early stages. In the lepromatous type the most marked changes occur when there is deep infiltration of the skin of the fingers. The nail becomes attenuated and there is longitudinal ridging of the nail-bed. In the nutritional lesions of the neural type the nail is thickened and tends to split transversely. Trophic blebs and blisters on the hands are frequently the result of burns and bruises to which the anæsthesia exposes them.

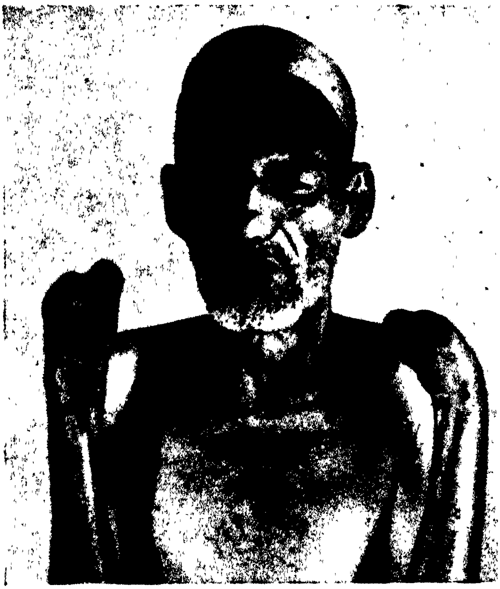


Fig. 88. Late effects of nerve-leprosy of 22 years' duration. *(Dr. H. K. Giffen)*

Muscles.—Muscular atrophies are most conspicuous in the neural type, chiefly from involvement of the ulnar nerve. Thus, the intrinsic muscles of the hands are affected, with flattening of the thenar and hypothenar eminences so characteristic of ulnar palsy. The characteristic *main-en-griffe* is a later development, with hyperextension of the metacarpo-phalangeal and flexion of the interphalangeal joints. The whole deformed hand becomes rigid, as if carved out of wood. Finally, with overgrowth of the nails and progressive osteoporotic changes in the phalanges, it becomes the typical leprous claw hand, like some deformed vulture's talon. Wrist drop may develop, chiefly from disuse ; as the bones shorten, a claw-like nail may often be implanted into a metacarpal. There is seldom any affection of the upper arm (Fig. 87).

Bones.—Decalcification and osteoporosis of the bones accompany the neural form. The phalanges become atrophied, and may actually become absorbed without sepsis or open wound. The metacarpals are less often affected. The process is often complicated by sepsis. and consequently necrosis of bone (Fig. 88).

Lymph glands.—In skin leprosy there may be enlargement of the axillary or inguinal glands. This may be due either to invasion of *Myco. lepræ* or septic organisms.

Lower extremities.—Initial lesions in natives commonly occur on the feet, and a patient may suffer from the more chronic types without noticing much amiss. Often the first sign noted is a bleb or blister. The superficial peroneal nerve, as it passes round the head of the fibula, is specially affected and is felt as a thickened and palpable cord. Drop-foot resulting from peroneal paralysis is not uncommon. The posterior tibial nerve is also frequently involved. The pretibial skin is stretched. shiny and hairless ; it does not sweat but usually becomes excessively dry and cracked. In others, again, there is elephantoid swelling of the feet extending to the knees, with depigmented anæsthetic patches, horny hyperkeratosis and mutilation of the toes.

Perforating ulcers of the soles of the feet are painful and crippling ; they are associated chiefly with neural cases and are the direct result of nerve involvement. The epithelium of the sole becomes thickened and inelastic. This leads to fissuring of the skin and the formation of ulcers. The feet become flattened and painful, owing to destruction of the musculature of the arch, and the anæsthesia may permit many injuries. Trophic changes in the muscles and periosteum lead to decalcification and absorption of the bone, which may be even more extensive in the foot than in the hand. Thus, the astragalus is often completely absorbed. Sepsis through cracks and abrasions is a terminal event. Nodules on the legs are most frequently found at the sites of injury or friction. They are especially common on the internal and external malleoli. Lymphangitis in the lower limbs is not uncommon.

Body and internal organs.—Lesions on the trunk do not differ in any essentials from those on the extremities. The middle line is less affected as a rule. Lesions on the front of the chest are said to be comparatively rare. In nerve leprosy typical herpetic lesions containing *Myco. lepræ* have been reported. Induration and even hypertrophy of the nipples are very common in the reactive stage, followed by retraction in the phase of resolution. It is said in India that, when the lower abdomen is protected by a loin cloth, lesions of the abdomen are confined to the upper half (Fig. 89).

Lesions of lungs have not been recorded. Large quantities of purulent sputum are due to bursting and discharge from nodules in the trachea and upper bronchi. Pulmonary tuberculosis not infrequently complicates the more severe forms of leprosy. Lepra bacilli are commonly found in spleen and liver, but do not seem to give rise to any special symptoms.

Genital organs.—Testicles are affected in advanced cases. Sterility is more common in males than in females, and it is rare for the ovaries to be involved. Swelling of the male breast (*gynæcomastia*) commonly occurs in cases in which the testes have been destroyed. The birth-rate amongst lepers appears to depend on the fertility of the male.

Lymphatic glands are enlarged in the vicinity of gross infections of a part, especially in the neck, axillæ and groin.

Resolution.—Leprous lesions may resolve spontaneously. Major tuberculoids may disappear, with deposition of scar tissue. Minor tuberculoids often heal up at the centre, with little change in the texture of the skin. In the lepromatous type, nodules which resolve leave flat scars like deep burns.

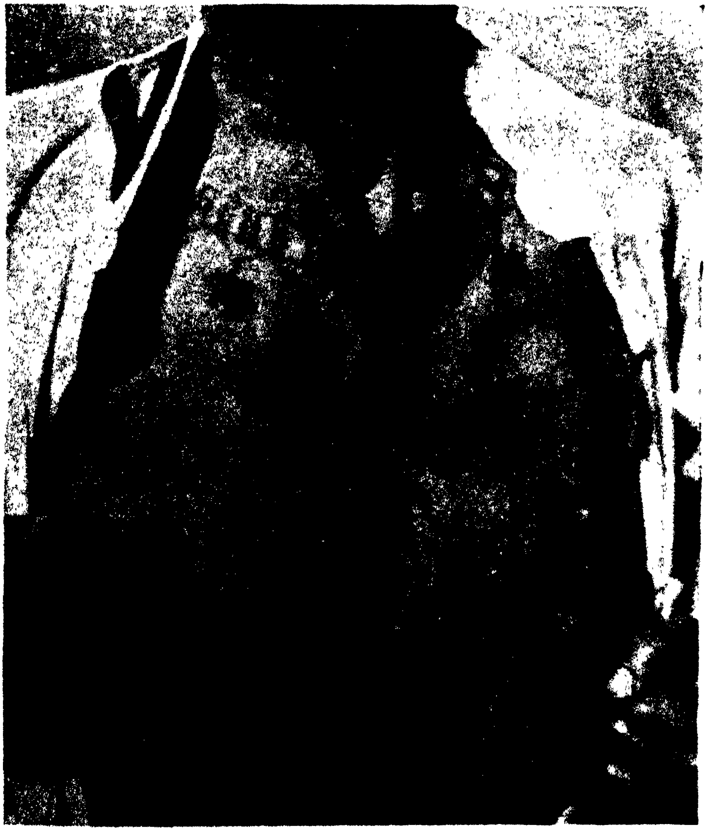


Fig. 89.—Leprosy, showing hypertrophied nipples.

Incidence.—Leprosy is more common in men and assumes a more severe form. In Norway the few remaining cases are chiefly in females, which is explained by their greater longevity and the milder character of their disease. Before the age of puberty children of both sexes are almost equally affected. The periods of puberty and childbirth impose a severe strain and increase somewhat the incidence in the female. The chief factor in the considerable excess of male cases is the greater freedom they enjoy. As in tuberculosis, the majority of cases are infected during the first two decades, and probably few contract the disease after 40.

Little is known about the factors of race, susceptibility and resistance. Differences which have been observed are probably explicable on climatic, social, dietetic and economic grounds. In India and Africa leprosy is especially common and severe in races with mixed European blood. That the social condition has a marked influence on the incidence and severity of leprosy is self-evident. In Norway it was formerly confined to fisher-folk living under very primitive conditions, but in India wealthy and highly-placed people are quite commonly infected. Rogers is of the opinion that in these it is a result of bed-infection.

Duration.—When leprosy is acute and febrile it may be fatal within two or three years, but in the great majority the course of the disease is very slow.

Diagnosis.—Early diagnosis is of the utmost importance, but many factors militate against it. It is, of course, easy to diagnose obvious and advanced cases. The ignorance of the patient, his dread of the disease, and the fear and superstitions of the general public may hinder prompt recognition. The earlier indications are the discoloured patches on the skin, and symptoms referable to involvement of the peripheral nerves, such as tingling or numbness, formication, or a feeling of woodenness in the limbs. In the majority of cases the first lesions noted are depigmented anæsthetic patches. Of fundamental importance are impairment of sensation, thickening and tenderness of nerves and demonstration of acid-fast bacilli.

To test sensation, the patient should be stripped and blindfolded. For testing anæsthesia to light touch, a feather should be used ; analgesia is tested by pin-prick ,using an area of normal skin as control. Loss of thermal anæsthesia is important. Hyperæsthesia and paræsthesia may precede anæsthesia to light touch.

Thickened nerves may be felt on palpation, and tenderness elicited by striking an area sharply with the finger or patellar hammer. The ulnar nerve is commonly affected above the elbow, the superficial peroneal at the head of the fibula behind the knee ; the radial as it curves round the humerus, or its branches as they pass over the lower end of the radius ; the posterior tibial below the inner malleolus ; the great auricular as it runs parallel to the external jugular vein and the branches of any particular nerve supplying a tuberculoid lesion. Examination of a smear for *Myco. lepræ*, by cutting down on the epineurium of a nerve, may occasionally be necessary.

Bacteriological examination.—In tuberculoid macules bacilli are difficult to find, and should be sought at the margins. In the lepromatous form, where there are no outstanding nodules, the lobule of the ear is the site of choice. Lymphatic gland puncture, as well as the examination of blister fluid by carbon dioxide snow, may be useful.

Biopsy of the skin may be made by smears made from a "snip" or by section. The scraped incision method of Wade consists of pinching-up the skin and applying compression to stop bleeding. With a small scalpel a cut 5 mm. long is made well into the infiltrated layer. All blood should be wiped away and, with the blade transverse to the incision line, the side and bottom of the cut should be scraped repeatedly, and the material spread on a slide and examined. The selection of the site is important, though *failure to find bacilli in one smear does not justify a negative diagnosis.*

Examination of the nasal mucosa is as important as that of the skin, and frequently a positive result is obtained when the skin is negative. A sharp-pointed tenotomy knife is the best instrument, and material should be sought in the septum and inferior turbinate. If there is ulceration, slight scraping suffices. Otherwise, a small piece of mucous membrane should be scraped off. Cotton swabs should not be used, as they frequently harbour saprophytic acid-fast organisms which may be mistaken for *Myco. lepræ.* The standard Ziehl-Neelsen method should be used for staining.

Rubino's reaction.—The blood sedimentation is constantly increased in leprosy and, concurrently, the cholesterol content of the blood is reduced (Westergren's method with citrated blood). Rubino has advocated an agglutination-sedimentation test with formolized sheep's corpuscles. The serum is said to contain a specific substance which causes rapid agglutination and sedimentation of these corpuscles. It is claimed that the reaction is specific and sedimentation is produced in less than one hour.

The lepromin reaction (Mitsuda).—In early lepromatous cases this reaction is usually positive, and resembles clinically and histologically the Mantoux reaction in tuberculosis, but it may not become apparent for several days (p. 577). It is an allergic response. Ota and Nitto have recently advocated, as giving better results, an antigen prepared from granulomatous deposits in the heart muscles of hens injected with human leprosy material. Cochrane found the lepromin reaction positive in 60 per cent. of neural and 100 per cent. of tuberculoid cases. Lepromatous cases are usually negative. Some healthy children give false positive reactions.

Subsidiary signs.—Anidrosis, often preceded by hyperidrosis, is characteristic of chronic cases, and is usually present in tuberculoid macules. In doubtful cases pilocarpine, 1 in 1,000 solution, is injected intradermally in a suspected patch and a similar amount in adjacent healthy skin. Both areas are then painted with tincture of iodine and, when dry, powdered with starch. The control area sweats, turning the starch blue. Absence of sweat at the point of injection indicates leprosy.

The histamine test of Rodrigues is somewhat similar in slight or early cases. A drop of 1 in 1,000 solution of histamine is placed within the margin of the suspected area, and a second outside. A prick is made with a needle through the drop. A red flare appears in normal skin.

Parakeratosis, hyperkeratosis, ichthyosis and alopecia.—These first three conditions are interconnected and are due to malnutrition followed by changes in the stratum corneum. The surface of the skin is shiny with scales. Hyperkeratosis is best seen on the palms of the hands and soles of the feet where the epithelium becomes abnormally thick and is apt to split, forming a superficial perforating ulcer. Somewhat similar changes take place in the nails, whilst loss of hair in the beard, eyebrow area and scalp are well known.

Differential diagnosis.—The characteristic marks of leprosy are sufficiently distinctive, but they have to be differentiated from psoriasis, seborrhœal dermatitis, various forms of tinea, eczema, lichen ruber planus, pellagra and filarial disease. Blastomycosis produces skin lesions reminiscent of leprosy. From syphilis and yaws, however, it may not always be so easy. Syphilitic and yaws skin lesions may often closely resemble the maculæ of leprosy, but the absence of sensory changes and reaction to treatment are sufficiently distinctive. The Wassermann reaction alone cannot always be depended upon in differential diagnosis. Syphilis and leprosy frequently co-exist. In mild early cases of leprosy positive reactions denote coincident spirochætal infection, but in advanced cutaneous and neural cases, especially those subject to lepra fever, a positive reaction does not necessarily always indicate a syphilitic infection. Lloyd, Muir and Mitra reported that 68 per cent. of nodular and 27 per cent. of neural cases in adults gave positive reactions.

The thickened skin of crab yaws on the feet may roughly resemble leprotic hyperkeratosis and may give a semblance of anæsthesia. Gangosa of yaws may be mistaken for nasal leprosy.

The early lesions of *mycosis fungoides* might possibly be mistaken for early nodular leprosy, and *leucoderma* is not infrequently associated with leprosy in the popular mind. It is extremely common, especially in India, and in negro races, and unfortunate sufferers are sometimes to be found in leper asylums. Depigmentation in the leucoderma, however, is more complete and sensory changes are absent. *Lupus vulgaris* is very likely to be mistaken for leprides, and in both diseases acid-fast bacilli are difficult to demonstrate. Lupus evinces a greater tendency to scar formation and there are no sensory changes.

Cutaneous leishmaniasis and, in South America, *espundia*, may be mistaken for leprosy. The lesions on the skin of the face tend to concentrate round the mouth and nose and form a more raised margin than those in leprosy. Demonstration of the Leishman-Donovan body will always settle the matter, but leishmanial lupus-like lesions on the ears may cause difficulty (*see* p. 175). *Acrodynia*, burns and other injuries may leave behind anæsthetic scars.

Neural leprosy has to be differentiated from *syringomyelia*, in which analgesia and loss of heat sense are accompanied by retention of sense of touch and normal sweat function. The absence of nerve swelling and tenderness is important. The nerve injuries caused by *cervical rib* may possibly be called into question, but can be settled by X-ray examination. *Raynaud's disease* has been confused because of trophic changes ; *hypertrophic interstitial neuritis* (Dejerine-Sotta's disease) may cause confusion ; this is a rare condition with thickening of nerves which may be so great as to render them conspicuous, and is accompanied by sensory and trophic changes, as in neural leprosy, and ultimate production of claw hand. *Von Recklinghausen's disease* (neurofibromata) may sometimes resemble leprosy.

Prognosis.—Leprosy may sometimes be a slight passing ailment, or may become the most repulsive loathsome disease known to man. The two important factors are concentration and distribution of bacilli in the body and resistance. Prognosis is more favourable in the neural than in the lepromatous type. The maintenance of a high standard of general health constitutes a most important element in prognosis. Some patients, even with advanced nodular lesions, are known to have partially recovered. On the whole, the earlier a patient comes under treatment the more favourable the prognosis. On account of the ease with which improvement in muscular power and in sensation can be determined, it is usually easier to assess the progress of the neural than of the lepromatous type. Very spectacular changes are most often seen in patients with tuberculoid lesions.

The danger of contact.—The factors which predispose to the danger of contact are closeness and duration, the infectivity of the case, combined with the age and general health of the person exposed to contagion. A child may acquire the disease after even slight contact.

Recovery.—In early neural cases progress may be stayed or arrested with little or no deformity. But there is no acid test of absolute recovery, and it is said that in such an arrested case, some severe intercurrent disease may herald return of leprosy. From the patient's viewpoint the main thing is whether there will be permanent deformity.

Causes of death.—Leprosy differs from tuberculosis in its low mortality. As a rule the victims do not die of leprosy so much as from intercurrent disease. They die from complications or as the result of crippling deformities. Death may be due to asphyxia from obstruction of the larynx or trachea, or to prolonged lepra fever.

Technique of the lepromin (Mitsuda) test.—Material is obtained by removing large, soft, nodules which are boiled in water for 20 minutes and divided into fine fragments with scissors. The epithelium is then removed and the material dried for a few hours with an electric fan, then in a vacuum desiccator over pure sulphuric acid. The dried material is ground up to a fine powder in a glass mortar and stored in a desiccator. In preparing the suspension 0·4 grm. of the dried powder is ground up with 10 c.c. of saline and the fluid pipetted off, a process which is repeated three or four times. Carbolic acid (0·5 c.c.) is then added and made up with normal saline. The suspension is made up in 1 c.c. ampoules, sealed and heated at 120° C. for half an hour. Standardization is difficult.

A series of intradermal tests with full strength lepromin are made in dilutions of 1 in 2, 1 in 4, 1 in 8. Stronger suspensions, as a rule, give stronger reactions. A standard smear is made and the number of bacilli estimated. The skin on the inner aspect of the arm is chosen, the customary dose being 0·2 c.c. The injection must be made intradermally; a slight serous effusion follows it, but disappears after a few days.

In positive cases a nodule appears at the site of inoculation between the first and third weeks, increasing in size up to a maximum. The degree of reaction is read by measuring the size of the nodule by a sliding calliper. In strong reactions there may be slight necrosis. In healthy adults not infected with leprosy the nodule is 6–10 mm. but in resistant cases it is much larger. The lepromin reaction is of use as a means of testing natural resistance to leprous infection.

The iodide test.—This test is of value in assessing the infectivity of cases when repeated bacteriological examinations of skin and nasal mucosa have given negative results. It should only be used, however, when the general health is good and when the blood sedimentation tests are within normal limits. A single dose of 2 grm. of potassium iodide in a glass of water is given at night. This may cause appearance of new cutaneous lesions or efflorescence of old ones, pain or tenderness of the nerves, pyrexia and increased sedimentation rate. The skin and nasal mucosa should then be examined for *Myco. lepræ.* If any reaction occurs, the next dose of potassium iodide should be delayed until it has subsided. If not, increasing doses of 4, 6, 8, 12, 16 grm. should be given at fourteen-day intervals, always with plenty of water. Should no further reaction occur, the leprotic infection may be regarded as arrested.

Treatment of leprosy.—*Chaulmoogra,* or *hydnocarpus oil,* has for a long time been employed as a remedy for leprosy in India and other countries. It is derived chiefly from the seeds of *Taraktogenos kurzii* (Assam and Burma), *Hydnocarpus wightiana* (South-West India), and *H. anthelmintica* (Siam and Indo-China). In recent years hydnocarpus trees have been introduced into Nigeria, the Congo, Fiji and East Africa. In Brazil a somewhat similar oil is obtained from *Carpotroche braziliensis* ("*Sapucainha*"). Though formerly given by the mouth, or by inunction, the more modern method is by injection. The oil itself, when expressed from fresh, ripe seeds of *H. wightiana* and *H. anthelmintica,* is well tolerated, but when stale acquires irritant properties. There is virtually no difference in the composition of chaulmoogra and hydnocarpus oils but, owing to the fact that the latter trees occur in more accessible areas and the seeds are easier to collect, hydnocarpus oil has largely replaced chaulmoogra in the official antileprotic oil of the B.P. (1932).

Sodium hydnocarpate (*Alepol*) (the sodium salt of a selected fraction of the fatty acid of hydnocarpus oil), introduced by Rogers in 1916, is soluble in water and can be given in 3 per cent. solution intramuscularly, subcutaneously and intradermally. If given intravenously it produces endophlebitis and sclerosis of veins.

The ethyl esters were introduced by Macdonald in 1920. Later, it was found that the esters of the total fatty acids of hydnocarpus oil, iodized to make them less irritant, were the most effective. The creosoted oils have been found to be almost as good and are well tolerated when injected.

Hydnocarpus oil and its esters intramuscularly, subcutaneously and intradermally are the most efficacious drugs, but the ethyl esters are more stable than the oil. They should not be exposed to air, but should be prepared and hermetically sealed in ampoules. The use of ampoules is recommended, but when stored in bottles the entire contents should be used on the day they are opened.

Esters must not be reheated. Various theories have been advanced for the action of chaulmoogra oil but none is generally accepted. Possibly it acts by its unsaturation as shown by its high iodine value. Other oils of high iodine value have been tried, amongst them codliver oil, linseed oil, and soya bean oil, but all have given results inferior to those of chaulmoogra.

Antileprol, ethyl ester of chaulmoogra, is dispensed in capsules of 1 grm. and given intramuscularly or by the mouth twice weekly in gradually increasing doses.

Moogrol (Burroughs, Wellcome) is also a mixture of ethyl esters of chaulmoogra, and is given by intramuscular injection. Commencing with 1 c.c. the dose is gradually increased to 6 c.c. at weekly intervals. It has also been given intravenously. The iodized ethyl esters are known as *iodized moogrol* and are usually given by intradermal injection, the leprotic lesion being completely infiltrated by producing coalescing " injection wheals." The dose is 1 c.c., gradually increasing to 5 c.c. It is recommended that tabloids of calcium iodoricinoleate (*Iodicin*) should be given by mouth three times daily, together with moogrol.

The mixture known as *E.C.C.O.* is composed of the ethyl ester of *Hydnocarpus wightiana*, creosote, camphor and olive oil and is given hypodermically in 0·5 c.c. doses, intravenously in 0·25 c.c. Total dosage is 7·5 c.c.

C. E. I. is a mixture of . . .	Chaulmoogra, 50 parts. Sulphuric ether, 50 parts. Iodine, 0·1 part.

The initial dose, intravenously, in daily injections, is 0·25 c.c., increasing gradually to the maximum, 1 c.c.

Modern workers regard the ethyl esters as less viscid, easier to inject and more rapidly absorbed. On the other hand, the viscidity of the oil is lessened if 4 per cent. creosote is added and if it is injected at 45° C. The oil is more stable and, when stored, is less liable to change, especially after addition of creosote.

Methods of administration.—The exact method—intramuscular, subcutaneous or intradermal—depends upon the type of case and condition of the patient. Intramuscular injections are preferably made into the gluteus maximus ; each dose should be divided, and not more than 1 c.c. injected at any given point. Divided injections are given partly by withdrawing the needle and reinserting at a different angle. By warming the oil, injecting slowly, and dividing the dose, painful indurations and abscesses may be avoided. Subcutaneous injections are made beneath lesions occurring on the more fleshy parts of the body, especially the extensor surfaces. The intradermal method, now much used, has the advantage that, in addition to the general effect, there is local action on the area infiltrated. This method is particularly suitable for the tuberculoid lepride. Two techniques are generally employed :

(1) The " plancha " method, used by American workers in the Philippines, by which multiple small fractional doses (0·05—0·1 c.c.) are injected intradermally, a small wheal about 5 mm. in diameter being raised round each puncture. By this method an area of 12 sq. cm. or more is infiltrated at one sitting by a short needle which enters the skin for 2–3 mm.

(2) A long thin needle is threaded through the skin to its socket, and the oil or esters injected as the needle is withdrawn. A successful injection should leave behind it a long wheal along the needle track, but there should be no re-infiltration of a skin area for one month, or at least until all induration produced by the last injection has resolved.

Doses.—Tolerance to hydnocarpus oil varies with weight, age and general condition. It is necessary to remember that each injection produces a negative phase of varying duration. The better the physical condition, the larger the doses the patient will tolerate. In estimating tolerance the blood sedimentation rate is important. The customary dose of the oil, hydnocarpate (*Alepol*) or esters, is from 0·5–6 c.c. once or twice weekly though occasionally doses up to 30 c.c. per week have been employed. It is usually administered as a 3 per cent. aqueous solution, commencing with 1 c.c., and rising by 0·5 c.c. to 5 c.c. In many cases it is better to give a proportion intradermally and the balance by other methods.

Special treatment should be continued until all active signs of the disease have disappeared, repeated bacteriological examination of skin and nasal mucosa are negative, and the nerves are no longer thick and tender. When active signs have definitely disappeared the disease is said to have become "quiescent," but when this state has remained stationary for two years it may be said to have become "arrested."

Special treatment aims at the destruction of *Myco. lepræ*; when they have practically disappeared from the body, the deformities can be relieved, but sensation can never be restored in permanent lesions. Compulsion is out of the question and patients must co-operate willingly. They should be encouraged to come as early as possible, and should be warned from the onset that treatment must necessarily be protracted.

Lepra reaction.—If this reaction occurs during the course of intensive treatment the injections must be stopped, but if there is some complicating disease (such as malaria) this must be specifically treated. During the lepra reaction the patient should be confined to bed and the bowels freely evacuated. Alkalies are advisable: 60 gr. of *sodium bicarbonate* may be given four times daily. Intravenous injection of potassium antimony tartrate, $\frac{1}{3}$ to $\frac{1}{2}$ gr. three times weekly, has proved an effective desensitizer. Intravenous injections of mercurochrome (3 c.c. of freshly made 1 per cent. solution) may sometimes control the condition. Calcium lactate and calcium gluconate in large doses act as adjuvants. Intravenous injections of aniline dye—trypan blue and methylene blue—have also been employed.

Treatment of pain.—Pain is usually associated with the lepra reaction, and there is increase of pain and tenderness in the distribution of affected nerves. For this, adrenalin hydrochloride 1 in 1000 solution (0·2–3 c.c. in 5 c.c. saline) is infiltrated into the perineural tissues, or alternately 0·02 grm. of ephedrine sulphate (dissolved in 10 c.c. of a 0·5 per cent. sodium bicarbonate solution) given by the mouth or injected similarly round the nerve usually gives relief. Snake venom in small doses has also been found useful. In leprous neuritis, with œdema of hands and feet, aneurin (vitamin B_1), in 10 mgm. doses daily, is said to be successful.

Surgical treatment.—*Excision of lesions.*—If there is only one small skin lesion, say less than 1 inch in diameter, it should be excised. Large outstanding nodules should be shaved off, the base being touched with strong carbolic or nitric acid. The electric cautery or carbon dioxide snow have been similarly employed. The treatment of perforating ulcers is a difficult problem. Necrosed bone should be removed. Chronic ulcers with indurated margins may be stimulated by infiltration with hydnocarpus esters, and by applying sulphonamide powders or paste. Amputation is seldom necessary.

When the thickened ulnar nerve is constricted by dense fibrous tissue behind the condyle, or the peroneal nerve is bound to the head of the fibula, the thickened band may be severed. The nerve sheath may be slit with benefit.

The eye.—If there is involvement of the iris, mydriatics (atropine) must be instilled to prevent further fixation. Particular care must be taken in the general treatment to avoid reactions which have an adverse effect on the eye. It is said that infiltration of the bulbar conjunctiva with a 1 in 1000 solution of trypan blue relieves the pain and congestion. But the best permanent results are obtained from improvement in the general health.

When there is anæsthesia of the cornea, paresis of the lids, or ectropion, the eyeball has to be protected with liquid paraffin, and a cotton-wool pledget should be tied over it at night. Sometimes the condition may be improved by marginal tarsorraphy.

The nose.—Special treatment is often required for the nasal ulceration, The crusts should be removed and the mucous membrane anæsthetized with cocaine and adrenalin or some caustic, such as trichloracetic or chromic acids (1 in 10 solution), applied and fulgurated with a diathermy apparatus. Sometimes douching with 2 per cent. sodium bicarbonate solution and painting with iodized hydnocarpus esters is also useful. For offensive discharge the following nasal lotion is used :

B. Sodii chlorid.	*aa* gr. 22 (1·42 grm.)
Sodii bicarb.	
Pot. chlor.	ʒ 2 (7·78 grm.)
Calc. phosph.	℥ ½ (15·5 grm.)

Sig.: ½ oz. to be used with ½ pint of water as a nasal douche.

Deformation of hands and feet.—Rehabilitation measures, such as carefully planned exercises, can often lessen deformities. The necessary movements may be produced in agriculture or textile industries, as carried out in the model Culion Island Colony in the Philippines.

Trophic ulcers.—Cochrane advocates filling the cavities with 5 per cent. sulphonamide paste, bandaging or strapping and leaving for one week. The following is recommended :

Sulphonamide (Sulphapyridine)	gr. 75 (5 grm.).
Adeps lanæ	ʒ 18 (70 grm.).
Liq. paraff.	ʒ 6½ (23 c.c.).

Operative procedures are sometimes necessary. Metatarsalectomy is advocated. The limb should be devasculated by a tourniquet, and the bone disarticulated before removal. Local anæsthesia, adequately given, suffices, and the tourniquet should not be removed until the wound has been well packed with sulphonamide paste and a tight bandage applied.

Subsidiary measures.—The production of protein shock by intravenous injections of milk or other forms of protein sometimes causes temporary improvement and aids in healing up intractable ulcers, but must be used with caution. The grounds on which these methods are based are the favourable results which sometimes follow febrile reactions in leprosy. Row in Bombay recorded such improvement after weekly subcutaneous injection of carbolized cultures of tubercle bacilli. Intravenous injections of killed *Bact. coli* (*pyrifer*) raise the temperature and cause a reaction, and good temporary results have followed the similar use of typhoid-paratyphoid vaccine in graduated doses, commencing with 50 million and gradually increasing to 200–300 million organisms in order to obtain satisfactory reactions.

Somewhat analogous results have been recorded from time to time by autogenous vaccines made from ground-up lepromatous material, and other acid-fast organisms grown from leprous nodules. The so-called anti-lepra serum of Rienstierna was obtained by injecting such a culture into sheep. Rapid and favourable action has been claimed by some observers as a result. X-rays and radium have also been tried, and various baths, such as iron, copper sulphate and iron arsenical baths at a temperature of 110° F. (in Java).

Some mention must be made of the recently-developed sulphonamide (promin) in treatment (Dinan, Pogge and others, 1943). This is the best of all preparations so far tried and has given encouraging results. The oral administration is toxic, and larger doses are tolerated by the intravenous route. By this method 1–5 grm. are injected daily for six days a week. The majority of cases have received the larger dose for months, with short intervals of one to two weeks three times yearly. The concentration in the blood declines rapidly, only traces being found 6–8 hours after injection. The toxic effects are anæmia in 46 per cent. after six weeks. The blood must therefore be watched, but responds to liver and iron preparations. Leucopenia was noted in 3 per cent. Allergic dermatitis and rhinitis may ensue. There is no evidence of any bactericidal action. After a year's treatment in 22 cases, 15 were definitely improved. Promin acted favourably on leprous keratitis, iridocyclitis and ulcers.

Prophylaxis.—If children could be prevented from coming into contact with infectious cases then the number of adults who would later become victims would be so few that the leprosy would decline. In planning preventive measures the incidence of child infection and of infectious lepromatous cases should be ascertained. If the former should reach 25 per cent. of the total and 20 per cent. of the latter, then intensive preventive measures must be undertaken.

The patients must be segregated in special areas near villages connected with a properly equipped centre. Infective cases in towns can be isolated solely in institutions. General hospitals should be prepared to treat leprosy in out-patient centres set apart for this purpose. Special research units should be developed, and special measures instituted for the care, segregation and observation of children with leprosy. Propaganda and carefully planned special training are essential.

A model leper colony is situated on Culion Island in the Philippines. It is a town with laundries, theatre and schools where some 8,000 lepers were originally segregated ; at the end of ten years the numbers had been reduced to 3,000 by natural causes and almost complete cessation of new infections.

Since improvements have been made in the dietary, and intensive treatment has been given with ethyl esters of chaulmoogra, especially good results have been obtained in children.

In no country should lepers be permitted to beg in the streets, keep shops, or handle food.

CHAPTER XXXII

YAWS (FRAMBŒSIA)

Synonyms.—Pian; Frambœsia; Boubas (Brazil); Coko (Fiji); Parangi[1] (Ceylon); Dube (Gold Coast); Purru (Malaya).

Definition.—Yaws is a contagious inoculable disease, characterized by primary sore and indefinite incubation period, followed usually by fever, rheumatic-like pains, and the appearance of papules which generally develop into a fungating, encrusted, granulomatous eruption. Running a chronic course, it usually protects against a second attack. The disease is caused by *Spirochæta pertenuis*, and is controlled by salvarsan and bismuth salts. The organisms of yaws and syphilis are indistinguishable and the lesions produced are extremely difficult to differentiate.

History.—The first descriptions, by Oviedo, of what we know as yaws did not appear until the sixteenth century. Before this period allusions in the literature appear to be mere surmises. Deductions from historical records suggest that yaws is of more ancient lineage than syphilis. It is clear that what we now know as syphilis appeared with dramatic suddenness at the end of of the fifteenth century and, as a new and devastating disease, spread rapidly over Europe. According to records, the disease broke out after the return of Columbus to Spain. Oviedo (1478–1557) was in Barcelona at the time, and in his *Historia General y Natural de las Indias*, he stated that it was contracted from Indian women by the Spaniards who accompanied Columbus, that it was brought by them to Spain, and transmitted to the army of Charles VIII. Las Casas (1474–1556), in his *Historia de las Indias*, refers to a disease which was very dangerous to Spaniards, and was known as syphilis, being known in Italy as the "French malady." Dias de Isla, a physician practising in Barcelona in 1493, gives a very complete account and states that it was unknown before that year, and that it was brought by the crew of Columbus on their return from the *first voyage* to Haiti. Dias himself treated several sailors from the squadron, including the pilot, Pinçon of Palos.

In the autumn of 1493, Charles VIII of France invaded Italy with a rabble army. He captured Naples on February 22, 1495, but a new plague (syphilis), accompanied by severe skin lesions, broke out and necessitated the evacuation of the city. The spread of syphilis can be traced, according to Pusey (1933), with the dispersal of Charles's army throughout Europe. In 1497 it reached England and Scotland. In Japan it was not recognized till 1509 at Nagasaki, where it was attributed to Chinese and Portuguese sailors.

Syphilis, when introduced into a non-immune population, as in Uganda, in the nineteenth century, reproduced symptoms and manifestations recorded by our ancestors in the fifteenth; under these circumstances there is little doubt that syphilis can act as a devastating epidemic. According to the far-reaching researches of such authorities as Virchow (1896) and Elliot Smith (1930), no syphilitic bone of pre-Columbian origin has been discovered. On the other hand, Means (1925) and Williams (1932) have found the long bones of Indians showing evidences of syphilis in primitive races in North and South America; and the former found evidences of it in skeletons of the prehistoric mound-building Indians of Ohio.

---

[1] This word means "foreigner," a term applied by the natives to the European invaders of Ceylon.

It is known that yaws often occurred in epidemic form on board slave ships and it may well be that the disease has an African importation into the New World. Much has been written of the possible identity in former times of such diseases as the " button scurvy " of Ireland, " sibbens " of Scotland and " radesyge " of Norway and Sweden. It may well be that during the seventeenth and eighteenth centuries they represented a severe form of syphilis.

Recent views on the syphilis-yaws question.—In Jamaica, Turner, Saunders, and Johnson record that no cardiac disease has been encountered in yaws cases, and this has been confirmed by radiographic examinations. In their critical survey of yaws in that island, they brought forward several new points. The " attack rate " in adults is as great as in children, and yet nothing like congenital syphilis has been seen in Jamaican babies, and this is held as strong evidence against the identity of syphilis and yaws. Infants and children in Jamaica are more liable to infection than are adults, and 90 per cent. of cases contract the disease before they are fifteen years of age.

It may well be that yaws and syphilis have sprung from a common ancestor. In yaws it is probable that the spirochæte, under the more primitive conditions of the tropics, has spread from man to man by intimate contact, whilst the syphilitic spirochæte under more civilized conditions, where such contact is not possible, came to be communicated by the venereal route, thereby assuming a more virulent character and evolving (as do certain other spirochætes) neurotropic strains. Intermediate forms between the two classical forms of these diseases, which are so closely related as to be zoologically referable as " subspecies," undoubtedly have become evolved in time, as in the non-venereal childhood syphilis of the Arab tribes of the Euphrates and Iraq, known as " Bejel " (Hudson). This disease has been well described in Deir-ez-Zor in Syria, where there is a high incidence of syphilis but very little gonorrhœa. This syphilis is spread by personal contact, is of low virulence, gives a positive Wassermann reaction, and corresponds to the endemic syphilis of Asia Minor described by von Düring. The most frequent lesions are in the mucous membranes of the mouth ; but in other respects—in the special affinity for children, and in the production of hyperkeratosis and depigmentation—it resembles yaws, and circinate lesions of the soles of the feet, resembling crab-yaws, are common. Depigmentation of the dorsum of the hands resembles that described by Lacapère in Morocco, but Hoff and Shaby state that meningo-vascular lesions may still be observed amongst these peoples.

Geographical distribution.—Yaws is common in tropical Africa, West Indies, Ceylon, Pacific islands, Papua, the East Indies, and the Malay States. In India and China it appears to be rare. Children in the West Indies and Fiji are especially liable. During recent years it has become extremely prevalent in Kenya Colony, Tanganyika Territory, and Uganda, where it is spreading with great rapidity. On the other hand yaws has disappeared to a great extent from Guiana, Ceylon and Barbados, where it was previously extremely rife.

Epidemiology and endemiology. *Contagion and heredity.*—As yaws is highly contagious, all circumstances favouring contact with the subjects of the disease favour it. Simple skin-contact does not suffice ; a breach of surface is necessary. The knowledge that the secretions from yaws lesions could transfer the disease to another person was well known to the slaves of the West Indies, and they practised auto-inoculation in their children who did not show a generalized eruption.

The disease frequently commences in a pre-existing ulcer, the organism (spirochæte) being conveyed by flies to the previously lacerated surface (p. 978). Cases originate in certain dirty houses, the virus from previous yaws patients seemingly impregnating the floors and walls of the filthy huts. In this manner the disease may be, and in some cases no doubt is, acquired without direct transference from an existing case. In some countries, as in Ceylon, yaws is a disease of the flat, low-lying districts, while practically absent from the hill country; in Assam, on the other hand, it is more common among the hill tribes than among dwellers of the plain. Ramsay has shown in Assam that native hill people, who only exhibit obscure lesions, such as condylomata, while living at high altitudes, develop florid yaws when they come down to the plains. In Jamaica, Saunders and Kumm have emphasized the importance of rainfall and geological formations on the distribution of yaws. Wherever there is porous limestone there is little or no yaws.

Yaws is neither hereditary nor congenital. A pregnant mother suffering from yaws does not give birth to a child suffering from the disease, nor one which will subsequently develop yaws, unless the virus be first introduced directly through a breach of surface after birth. It is not conveyed by the milk; nor does a suckling suffering from yaws necessarily infect its nurse.

This statement should be qualified by the well-known fact that a syphilis-infected mother does not inevitably transmit the disease to her offspring, and if she does transmit, she may do so irregularly, not to one child, but to the next, and to one only of twins.

Although two-thirds of the cases in the West Indies, Pacific Islands and Ceylon occur before puberty, no age is exempt. In Jamaica the peak of the infection rate is about eight years. No new infections are found after thirty. Three males appear to be infected to every one female. It has been frequently remarked that yaws shows a predilection for certain native races. On the whole, the negro and negrito stock is specially liable to severe attack.

Yaws at the present day shows a striking limitation to the tropics, but it is a disease so readily communicable by direct contact that it seems remarkable that it does not spread in temperate regions. In the tropics yaws is limited to low level areas, and to rural districts with primitive sanitation. In Haiti, for instance, yaws is the disease of distant villages, and syphilis with chancre is common in the main town. In the Philippines the same is true: in the country, yaws; in Manila, syphilis.

Ætiology.—In 1905 Castellani demonstrated in scrapings of yaws tissues an extremely delicate spirochæte—*Spirochæta pertenuis*—very like that of syphilis. To demonstrate this spirochæte, slides should be prepared from scrapings of an incised yaw papule before it has ruptured. The films may then be stained with Giemsa, or made by the indian-ink method; better still, the living parasites may be detected in fresh undried films by darkground illumination. A fully developed yaw is unsuitable, because it has been exposed to external sources of contamination and a variety of organisms will be present and may confuse the observer. Dobell and others have been unable to distinguish any structural differences between this spirochæte and *S. pallida* of syphilis (Fig. 228, 5, p. 864).

S. pertenuis has been found in the spleen, lymphatic glands, and bonemarrow; doubtless it also occurs in the blood. It is inoculable into monkeys and rabbits; in the former, especially in the orang-outang, it gives rise to lesions similar to those in the human subject.

Cultivation of *S. pertenuis* was successfully performed by Noguchi in ascitic fluid containing a piece of fresh animal tissue, such as the kidney, the whole being covered with a layer of sterile paraffin. This rather complicated technique has been simplified by the later work of Hata, who substituted horse-serum, the inoculation being made through the upper solidified layer. Strict anærobiosis is necessary.

Kumm has brought forward strong evidence that in Jamaica, at any rate, a minute fly, *Hippelates pallipes*, carries the spirochæte from one person to another. He collected the flies at the rate of 5,000 per hour from one ulcer; they crawl under the scab and ingest large numbers of *S. pertenuis*, which are afterwards regurgitated. *H. pallipes* is an oscinid fly having peculiar mouth-parts, with projecting spines on the pseudotracheæ and labellæ (*see* p. 985).

Inoculation into monkeys.—The most extensive and minute observations of Schöbl on *Cynomolgus philippinensis* with emulsified extracts of yaws lesions containing *S. pertenuis* deserve mention. The injections were made on the nose, eyebrows and scrotum. From three to five weeks after inoculation, papules appeared, corresponding to the typical yaw. Later, they spread peripherally like the ring-worm form of this disease. The disease in the monkey on first inoculation runs its course without developing into diffuse secondaries, but generalized yaws is produced by superinfection. Other late manifestations, such as lupus-like ulcerations and keratoderma of plantar surfaces, resemble those seen in man.

Human inoculation.—The fact that the disease could be transferred by secretion from yaws lesions was well known to the slaves in the West Indies. Charlouis and others have inoculated yaws patients with syphilitic virus and have produced a chancre at a site of inoculation. Schöbl considers that *S. pallida* is panblastotropic with a tendency to invade and multiply in all tissues and produce lesions, but is mesoblastic in its tendencies. Syphilitic lesions are found in the skin, mucous membranes, bones and muscles, viscera and nervous system. The spirochætes invade the cardio-vascular system and enter the placenta, giving rise to congenital syphilis. The yaws spirochæte is epiblastotropic, invading certain tissues, particularly the skin and bones; the nervous and cardio-vascular systems are not usually invaded and the disease is not congenital. It is suggested that in the few instances in which lesions of the internal organs and cardio-vascular system have been reported, co-existing syphilis has not been rigidly excluded.

Yaws, moreover, shows a striking limitation to the tropics, and the effect of climate upon it is such that it does not spread in temperate climates from cases which are introduced. It is more common at low altitudes and in areas with higher rainfall.

Yaws spirochætes are unable to penetrate unbroken skin surfaces. Auto-inoculation may occur during the early course of the disease in man; the infection may spread to other parts of the skin, but mucous membranes are not invaded.

Other animal inoculations.—Nichols originally showed that yaws, like syphilitic lesions, can be produced in the testis of the rabbit, though the incubation period is shorter. Pearce and Brown observed, in intratesticular inoculation with *S. pertenuis* in the rabbit, a granular and finely nodular periorchitis, a lesion different from that of *S. pallida*. Turner and Chesney in Haiti found that in rabbits injected with *S. pertenuis* the testicular lesions consisted of miliary granules in the tunica and epididymis, but that general enlargement and induration (so common after inoculation with *S. pallida*) do not occur.

Pathology.—A feature of yaws lesions is the great thickening of the epidermis and degeneration in the epithelial cells. In later stages there may be hyperkeratosis. The elongated papillæ are vascular, and are infiltrated with lymphocytes; leucocytes and plasma cells are also numerous. In contrast with syphilis, perivascular infiltration in the corium is absent, and there is no endarteritis as in syphilis. Dupont and Dubois describe the primary lesion as an epidermic papule of which the centre becomes necrotic and leads to ulceration. Cellular infiltration is limited. In contradistinction, the syphilitic chancre erodes the epidermis and extends more deeply. In secondary yaws large papules are formed by inflammatory infiltration with hypertrophy of the epidermal ridges. In the gummatous stage the essential feature is dominance of the epithelioid elements in the infiltration.

Symptoms.—As in syphilis, the symptoms of yaws can be divided into three stages—primary, secondary, and tertiary.

PRIMARY LESION (*madra buba* or "mother yaw").—According to Sellards the *incubation period* in experimentally-inoculated yaws in man is three and a half to four weeks; in experimental apes it may be as long as three months. Naturally-acquired yaws is reputed to have, as a rule, a longer incubation period than the inoculated disease. The primary lesion may appear as a granuloma or a papule at the site of inoculation, 1–7 cm. in diameter, and is known as the "framboesoma." It may develop at the site of some old skin lesion. It is ordinarily extragenital, but may be situated on any part of the body: the buttock, thigh, knee, leg, arm, breast, or lip (Fig. 90), but is rare on the scalp. The lower part of the leg is the site of predilection; the breasts of nursing women and the mouths of suckling babies are not uncommon sites. In Moss and Bigelow's large series the genitalia were the seat of the primary lesion in only 1 per cent. In native women it is frequently observed at the bend of the elbow, or on the hip, and is contracted in this situation from carrying children who are infected with the disease. The primary lesion may be so small as to escape detection; it may be single or multiple, and, in fact, great difficulty may be experienced in differentiating it from allied cutaneous lesions, but, as a rule, it is remarkably persistent, lasting from two to four months, and it may persist for a year or more.

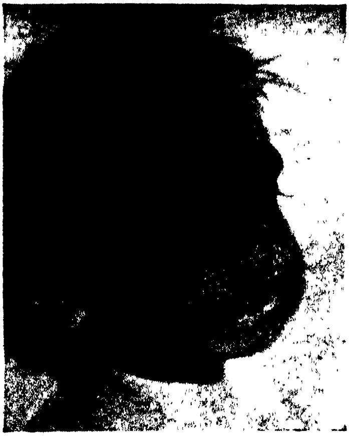


Fig. 90.—Primary yaws sore on lips of Australian aborigine child. (*Dr. H. Basedow, Adelaide*)

According to the Jamaican Yaws Commission, the primary lesion is found on the lower extremities in over 70 per cent. of cases. In 39 cases it was found:—

On head, face and neck in	1
On upper extremities „	4
On genitalia „	1
On leg „	12
On ankle and foot „	21

The lesion, on becoming larger, becomes covered with a yellowish secretion or scab. It is at this stage known as the "mother or master yaw," the "mama pian" of the French. In ordinary locations yaws lesions are not painful, unless firmly pressed.

The appearance of the lesion is preceded by a certain amount of constitutional disturbance. The intensity of the general symptoms varies within wide limits; sometimes they are hardly perceptible, so are not complained of, but usually there is well-marked malaise with rheumatic pains. Occasionally there is severe constitutional disturbance lasting for about a week, with rigor, smart fever (100° to 103° F.), persistent headache, pains—worse at night—in the long bones, joints and loins, and sometimes gastric disturbance and diarrhœa, especially in children. The lymphatic glands in the immediate vicinity become enlarged. During the decline of these constitutional symptoms the secondary eruption appears. The Wassermann reaction becomes positive three to four weeks after the primary lesion and rapidly grows stronger in titre.

Secondary stage.—This is ushered in by a fine, light-coloured furfuraceous desquamation. The skin becomes harsh and dry, loses its natural gloss, and here and there patches of desquamation (best appreciated with the aid of a hand lens) are formed. These patches are mostly small and circular; occasionally they are oval, irregular, or form rings encircling islets of healthy skin scattered irregularly over limbs and trunk; sometimes they are almost confluent, the patches coalescing and making the skin look as if it had been dusted over with flour. On the other hand, this furfuraceous desquamation may be so slight as to be overlooked. In some instances the heaping-up of desquamating epidermic scales produces white depigmented patches, very evident on the dark skin of a negro or oriental.

This patchy, furfuraceous condition of the skin may persist throughout the attack, or may reappear as a fresh eruption at any time in the course of the disease. It has been described by Schöbl and Sellards as "keratoid exanthem" in artificially-inoculated yaws.

Appearance of the yaw (Fig. 91).—When the furfuraceous patches have been in existence for a few days, minute papules appear in them. This very characteristic eruption, from which the disease takes one of its names—*framboesia* (or *raspberry*)—breaks out three months after the primary lesion. These secondary lesions may vary in size from a pin's head to half a crown and, according to Spittel, begin around the primary sore ("mother and daughter yaw"). The itching is usually considerable. As in syphilis, the eruption may be very pleomorphic; it may be roseolar, or consist of macules with desquamation resembling a squamous syphilide. It may appear on any part of the body, especially in exposed situations and on the anterior surface. The papules occur in groups, the larger appearing to be surrounded by a group of satellites, which has given rise to the various native designations for yaws. Auto-inoculation is probably responsible for the appearance of these lesions in symmetrical fashion, whenever the skin or mucous surfaces come into intimate contact; they are present at the angles of the mouth, in the axillæ, in the anal cleft, and in the inguinal region; in contradistinction to syphilis, they are rarely present on the true mucous surfaces, but often in clusters just inside the nostril. Several of the groups may coalesce to cover a surface.

The yaw is pushed up from the rete Malpighii through the horny epidermis, which breaks over the summit and splits in radiating lines from the centre, the necrosed segments curling away from the increasing papule. Soon a yellow point appears around a hair follicle, consisting of a cheesy-looking substance which cannot be wiped away, unless undue force is used.

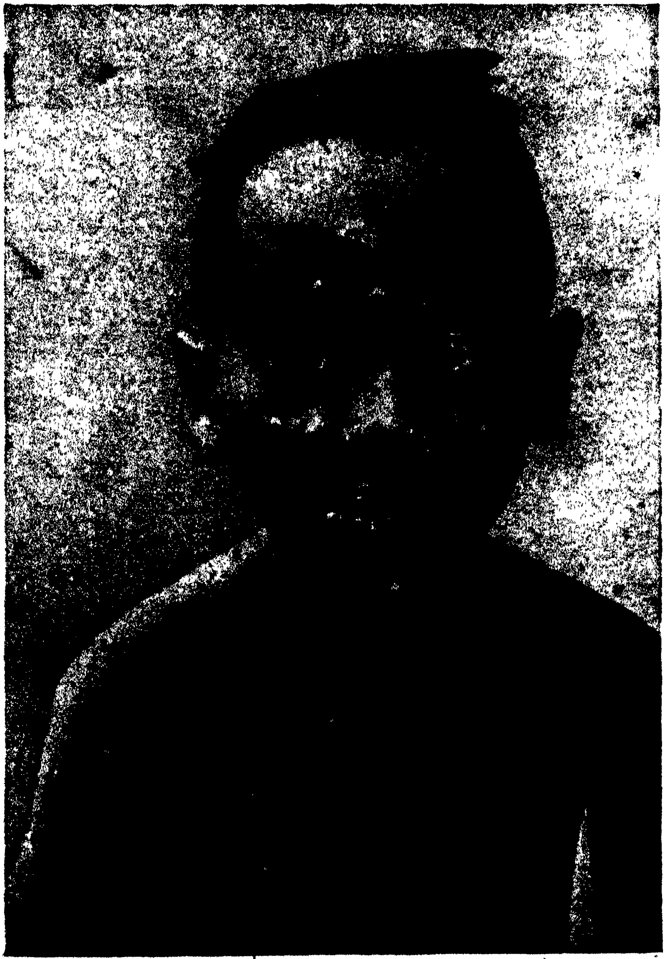


Fig. 91.—Secondary yaws in a Malay boy. (*W. E. Le Gros Clark.*)

From this stage the papule may either cease to grow, the apex becoming depressed, or may go on to form the typical yaw. In the latter case the lesion gradually grows into a rounded excrescence, the yellow material at the top widening out so as to form a complete cap encrusting the little tumour. The smaller tumours are hemispherical; the larger are more flattened, or even depressed at the centre, possessing everted, somewhat overhanging, rounded edges. Occasionally, though rarely, a big yaw may include an area of sound skin.

The firmly adherent crust which caps and encloses an uninjured yaw is yellowish, granular, blotched with blood-stains and encrusted dirt. Deprived of its crust, the little swelling is seen to be red, generally smooth and rounded on the surface, and oozing pale yellowish serum in which spirochætes may be demonstrated; when inspissated, this serum forms a fresh cap to the yaw, and on microscopic examination is found to be teeming with the organisms. According to size, it stands out anything from ⅛ to ¾ in. above the surrounding healthy skin. Pus, unless a consequence of irritation, is not, as a rule, found under the crust.

Although the formation of the papules and yaws is attended with much itching, the yaw itself is not at all sensitive; the tumour may be touched, with acid even, without causing pain—a diagnostic point of some importance. Sometimes, as in syphilis, the eruption has a circinate character, the so-called "ringworm yaws." The itching of yaws lesions is a point of differentiation from syphilis, but, as Blacklock has pointed out, native races are exposed to insect bites and dirt.

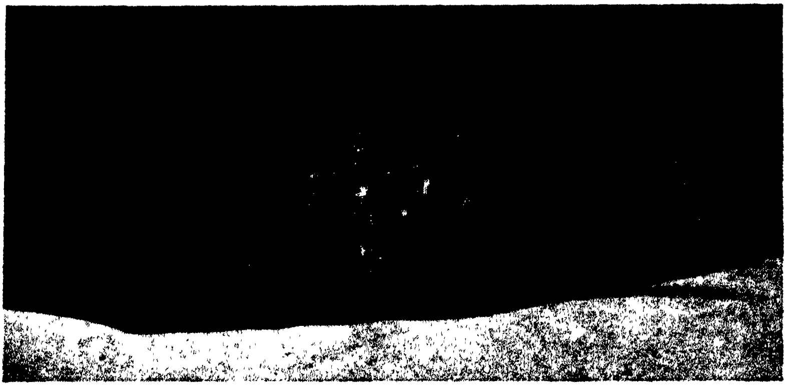


Fig. 92.—Tertiary yaws ulceration on forearm of European.

The yaw usually attains its maximum development in two weeks. For several weeks longer it remains stationary before beginning to shrink. The crust then thins, shrinks, darkens, separates at the periphery, and at last falls off, disclosing, at the site of the former fungating mass, a slightly thickened spot of fairly sound skin, which, though pale at first, may subsequently become hyperpigmented.

Sometimes the secondary rash takes on a papular appearance, when the lesions are known as "acuminate papules." These are symmetrically distributed over the back, shoulders, arms, elbows and knees, and much resemble a follicular syphilide. Secondary lesions may last from six months to a year. Simultaneously with the eruption, as in secondary lis, there may be a uniform, painless enlargement of the lymphatic s, in the aspirated lymph of which the specific micro-organism may be demonstrated. When the lesions subside, pigmented spots remain, as in secondary syphilis, and are specially noticable on the palms of the hands.

Lichenoid eruptions.—*Lichen frambœsianus* ("*Pian datre*") is a lichenoid generalized eruption of the skin described by Dutch writers in the East Indies. It is a micropapular eruption which is very striking in appearance and is not associated with *yaws papules*. It is, of course, analogous to secondary lichenoid eruptions in syphilis, and must be distinguished from other lichenoid eruptions, such as lichen ruber planus, lichen pilaris and lichen scrofulosorum. It is now generally recognized as an early secondary manifestation in children and young adults, the same condition as has been described by Nicholls as "furfuraceous desquamation" and by German writers as the early frambœsiform efflorescence. The lichenoid eruption is apt to occur in patches over the shoulders and, according to Deibel and Elsbach, there is a tendency to

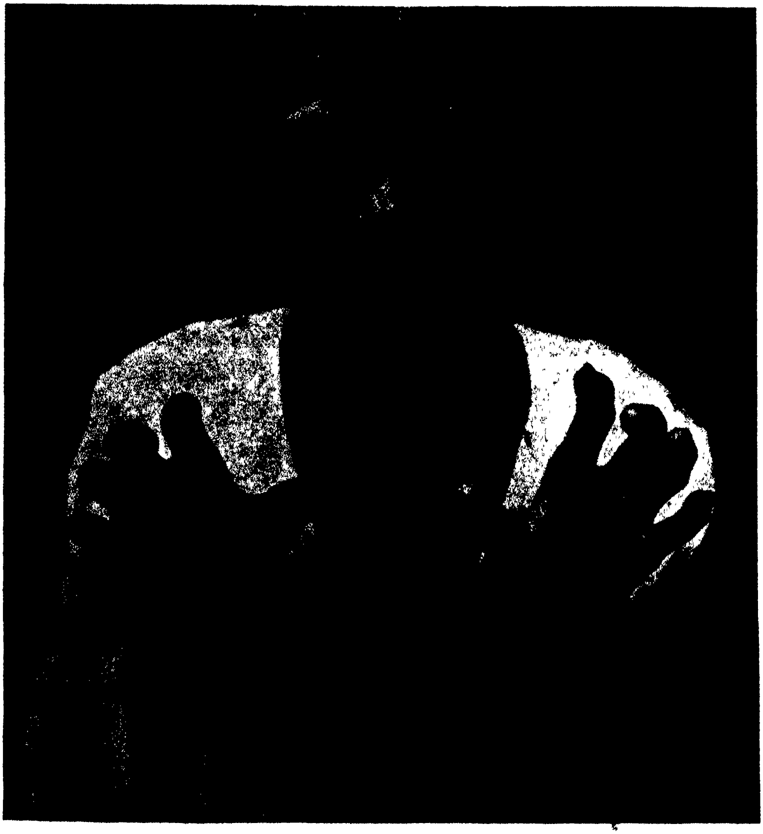


Fig. 93.—Tertiary yaws. Onychia of fingers.

hyperpigmentation of the peripheral micropapules, associated with depigmentation of the centre.

The serum of patients in the secondary stage gives marked positive Wassermann and Kahn reactions, and this makes the differential diagnosis from syphilis impossible by these means.

Tertiary stage.—It sometimes happens that the tumours, instead of becoming absorbed, break down and ulcerate, the ulceration, which may last for years, being confined to the yaw itself. In other instances ulceration goes deeper and extends circumferentially, giving rise to extensive sores with subsequent cicatrical contractions. Such ulcerations occur in about 8 per cent. of cases and may or may not be encrusted.

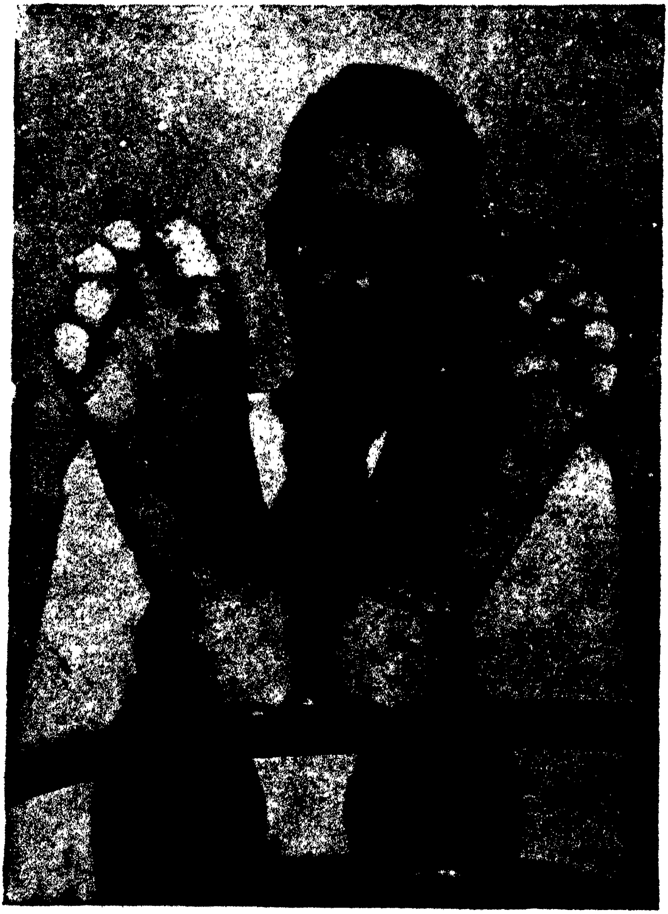


Fig. 94.—Foot yaws, or "crab yaws." (*Dr. J. D. Reed.*)

(Fig. 92.) With the development of the deeper and wider forms of ulceration, the typical lesions of yaws may disappear for a time, or perhaps permanently. In the latter case the ulcers are said to be non-infective. Ulceration of the greater part of the limbs, especially the leg and ankle, may take place. Tertiary manifestations are seldom observed in cases which present late secondary lesions. The serum of these cases gives positive Wassermann and Kahn reactions, but the cerebro-spinal fluid, in cases of advanced ulceration of the nose and other parts of the body, gives a negative reaction with a normal cellular and biochemical picture.

Lesions of the hands.—A scaly condition of the palms of the hands may persist for years. Multiple dactylitis, with uniform swelling of the phalanges, onychia, paronychia, atrophy of the nails, and subsequent deformity, is often observed. (Fig. 93.)

Foot yaws ("Dumas," or pink parangi—Ceylon; "crabs," or "crab yaws"—West Indies).—When a yaw develops on the sole of the foot it causes much suffering because it is bound down by the dense and thick epidermis. Spreading laterally under the thick, leathery and unyielding epidermis, it may become large. After a time the epidermis over the growth gives way, splitting up in a radiating fashion (Fig. 94). Pressure being thus removed, the yaw fungates, and suffering diminishes. Crab yaws may last a lifetime after infection in childhood. Chesterman suggests that in the foot lesions a fixation point for *S. pertenuis* is formed. A condition known as "clavus" in Dominica results from the healing of these granulomata; the centre of the core drops out, leaving an irregular erosion of the sole of the foot, or there may be deep fissures or cracks. Similar pitting occurs on the palms of the hands. According to Sayers, this is the commonest lesion of yaws in the Solomon Islands, and causes great disability, especially in children; when bilateral it incapacitates them from walking.

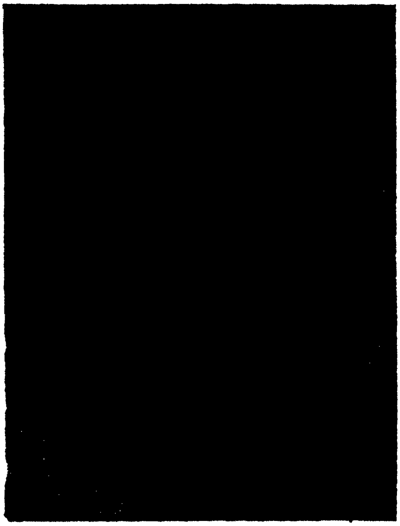


Fig. 95.—Gangosa in an Australian aborigine. (*Dr. H. Basedow, Adelaide.*)

Gangosa (derived from the Spanish meaning "muffled voice"), or destructive ulcerous rhino-pharyngitis (Fig. 95), which is now generally regarded as a sequel of yaws, usually commences as an ulcer on the soft palate. Slowly spreading, it may make a clean sweep of the hard palate, the soft parts, cartilages and bones of the nose, sparing the upper lip, which is left as a bridge across a great chasm, the floor of which is formed by the intact tongue. A most offensive odour is given off from the ulcerated surface. The disease may be arrested spontaneously at any period of its progress, and long before such extensive mutilation as that described has been effected ; but it is always a longstanding and chronic affair and may linger as an indolent ulceration for years. As a rule, the larynx is spared ; but although phonation may be retained, articulation is seriously impaired. Gangosa occurs at any age, but is rare in young adults, though Leyes states that in Guam he has seen it in children of 3, 4, and 9 years of age. It is very common in parts of the West Indies (Dominica, 60 cases in a population of 2,000), Guam (1·5 per cent. of the population), the Carolines, Fiji, Ceylon, British Guiana, and West, Central, and East Africa. It is often found associated with the bone lesions of yaws.

Goundou, or Anákhré ("*Gros Nez*").—In 1882 MacAlister drew attention to what were termed the horned men of Africa, and in 1887 Lamprey gave further details illustrated with drawings. The natives call the disease goundou and anákhré. Later observations show that it has a wide distribution in Central Africa and South America, and that a similar disease occurs in the larger apes, chimpanzees, and baboons. An ancient Inca skull from Peru, described by Letulle, shows the characteristic lesions of goundou.

Stannus and Hamerton have shown that in the apes the hyperostosis is probably the after-result of osteitis cystica.

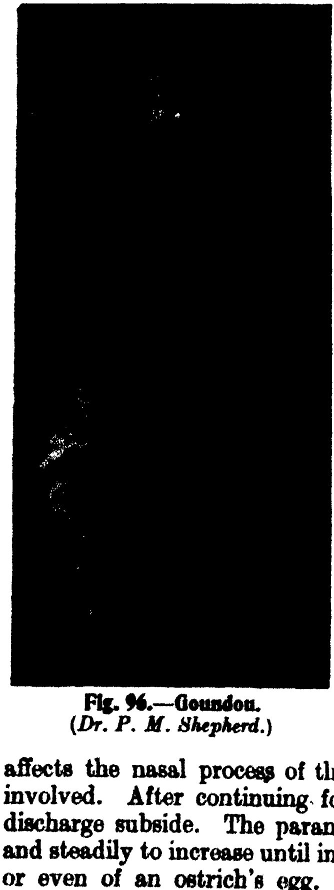


Fig. 96.—Goundou.
(*Dr. P. M. Shepherd.*)

Goundou usually commences during childhood, although adults may be attacked. The earliest symptoms are severe and more or less persistent headache which, after a time, is associated with a sanguino-purulent discharge from the nostrils, and formation of symmetrical swellings the size of a small bean at the side of the nose. Apparently the swelling affects the nasal process of the superior maxilla. The cartilages are not involved. After continuing for six or eight months, the headache and discharge subside. The paranasal swellings persist, and continue slowly and steadily to increase until in time they may attain the size of an orange, or even of an ostrich's egg. As they grow, the tumours, encroaching on the orbits, may interfere with the line of vision and finally destroy the eyes. In severe cases there is a general diffuse hyperostosis of the anterior part of the maxilla. There is no pain in the tumours themselves. The superjacent skin is healthy and freely movable. The tumours are oval, with the long axes directed downwards and slightly from within outwards (Fig. 96). The nostrils are bulged inwards and more or less obstructed. The hard palate is often affected, resulting in the most hideous deformity. General glandular enlargement may be noted. Trauma seems to predispose to the development of goundou.

A case of goundou associated with tertiary syphilis was described in London by Sharpe. The patient had never been in the tropics. The lesions resembled the paranasal swellings so characteristic of goundou.

According to recent accounts, cases of goundou in Jamaicans invariably give a positive Wassermann reaction.

The bony outgrowths, not necessarily bilateral, are attached to the nasal bone and nasal process of the maxilla, but, according to Botreau-Roussel and Clapier, they are not entirely confined to this region ; a similar hyperostosis may co-exist on the tibia, upper or lower jaw, forearm, femur, or clavicle. There is a general opinion at present that goundou is a systematized hypertrophic osteitis connected in some way with yaws.

The bony changes of goundou consist of hyperostosis, which may be limited to the ascending or nasal processes of the superior maxilla, or be more widespread and affect the other bones of the skull as well, with an ever-present tendency to the formation of bosses of overgrowth and to the obliteration of adjacent cavities. The underlying pathological process is an osteo-periosteal dyscrasia, and the end-result is the production of finely-porous bone.

As yaws and syphilis are so closely allied, it might be expected that similar lesions might be found in the generalized osteitis of syphilis, but there appears to be very little evidence of it. There is very little difference between the bony changes of goundou and those which have been called *leontiasis ossea*, and, according to Stannus, hyperostosis of the facial bones has also been recorded in Paget's disease—*osteitis deformans*. According to modern knowledge, it seems possible that goundou is more akin to *osteitis fibrosa*, due to interference with the bony metabolism and an endocrine disorder, and it may well be that in this instance yaws constitutes the non-specific factor acting on an ill-fed native child

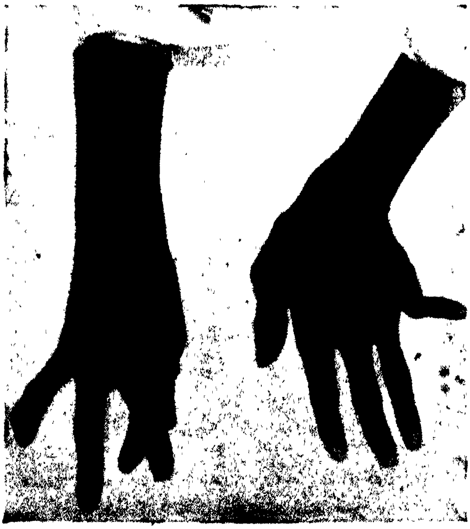


Fig. 97.—Distortion of fingers in tertiary yaws.

population. Goundou-like swellings in horses, monkeys and young pigs ("cachexie osseuse") point to osteitis fibrosa as the initial stage of this condition and all changes between cystic disease of the bones and hypertrophic exostosis can be traced in a series of skulls.

Treatment consists in incising and displacing the periosteum and chipping away the bony outgrowth with a chisel. Early cases, according to Botreau-Roussel, yield to intravenous and intramuscular injections of neosalvarsan, four or more injections being necessary before improvement is observed. This observer operated with success upon 118 out of 130 cases observed on the French Ivory Coast and the reader is referred to his monograph (Masson et Cie., 1925) for further information.

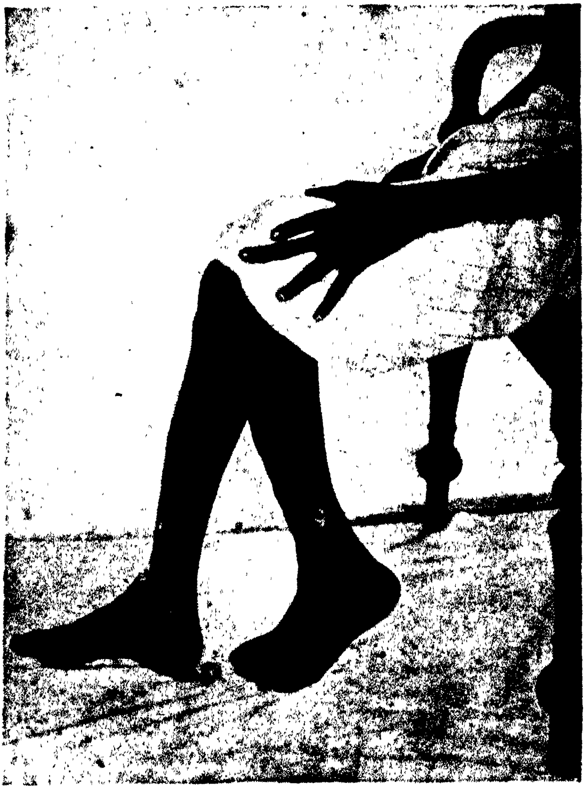


Fig. 98.—Tibial periosteal nodes, ulcers, and deformity of phalanges in yaws.

Periositis, osteitis and epiphysitis (Figs. 97, 98, 99).—Circumscribed painful periosteal nodes are frequently found on the anterior aspect of the long bones, especially the radius, ulna, and tibia. The swellings are hot and exquisitely tender, and the superjacent skin is tense and stretched. After the subsidence of the acute stage, hard, firm periosteal nodes remain. A diffuse osteitis may result in a sabre-shaped deformity of the long bones, especially the tibia and occasionally the arms and fingers. A rarefying process is also at work, for such bones are subject to spontaneous fracture with resulting malunion, accidents which are common in districts in which yaws is endemic. Hackett, who has studied the sabre-shaped tibiæ of the aborigines of Australia, believes that syphilis does not occur among these peoples, and that the bone lesions are due to yaws. Colloquially known as "boomerang leg," the deformity is an antero-posterior curvature below the knee with a forward convexity; occasionally there are bosses of localized periostitis. Radiographs show that areas of rarefaction appear early, and the bone becomes deformed. The appearances depend upon the severity of the initial lesion and the time which has elapsed since the onset of the disease. Other lesion of yaws, including gangosa, have been noted in Central and Northern Australia. A chronic periostitis of the clavicle is frequent in Fiji. These bone changes are accompanied by intense rheumatic pains, and have received distinctive names, such as "sasala."

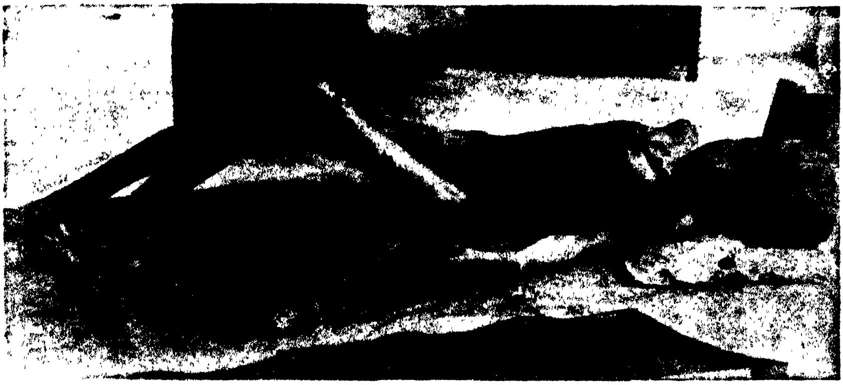


Fig. 99.—Sabre-like deformity of tibia, radius, and ulna, and multiple cutaneous ulcerations in yaws.

Juxta-articular nodules.—Fibrotic tumours situated over the olecranon, the lower end of the femur, and in other situations on the long bones, are now regarded as a tertiary phenomenon of yaws. Formerly they were regarded as constituting a disease *sui generis*, but those cases which have been investigated invariably give a positive Wassermann reaction. Originating subcutaneously, these nodules may reach the size of a small orange (Fig. 100). They are remarkably painless, and very rarely ulcerate or suppurate. Juxta-articular nodules are generally multiple, and usually in the neighbourhood of the joints, but, according to Steiner, may occur scattered over the body. Similar lesions have been described in tertiary syphilis, and the *Spirochæta pallida* has been isolated from them (Hu and Frazier), while Hudson found the same nodules in "bejel," the non-venereal syphilis of the Arabs, among whom they occur in 2·1 per cent.

of the adult male population and are known locally as "rik." According to Frontoynant and Girard, they contain uric-acid crystals. In Africa they are apt to be mistaken for *Onchocerca volvulus* cysts.

Skin lesions.—Healing of subcutaneous gummata is frequently followed by depigmentation of the skin, resulting in light-coloured or leucodermic patches, especially visible in native races. A macular depigmented exanthem limited to the hands, wrists, feet and ankles is pathognomonic of yaws and was first described by Ziemann as " melung."

After effects.—Contractions resulting from scar tissue may lead to partial ankylosis of joints, in severe cases to the destruction of lymph-channels and to the production of elephantiasis in the affected limb.

Synovitis.—Chronic synovitis, analogous to that of tertiary syphilis often associated with bone lesions, and, it may be, with disorganization of the joint, has been recorded.

Ganglion and other lesions. — The frequency of tenosynovitis and ganglion-formation in the region of the wrist was noted by Graham, Moore, and other observers. These ganglia are usually associated with tenosynovitis and, as extra proof of their origin, they both respond in a remarkable manner to treatment with neosalvarsan and bismuth. Stricture of the mouth due to tertiary yaws has been recorded.

The general health.—Except during the initial fever, or during one of the recurring febrile relapses, the general health is not, as a rule, affected. Occasionally, however, there are debility and cachexia ; or there may be enlargement and tenderness of the lymphatic glands. In other instances rheumatic pains may be very severe.

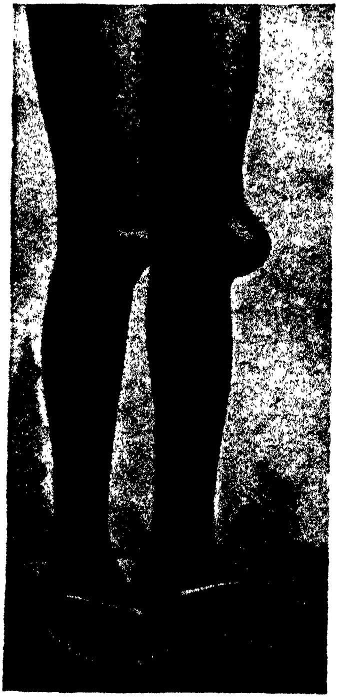


Fig. 100.—Juxta-articular nodules.
(*Photo : Dr. Watt.*)

Immunity.—After the subsidence of the secondary stage immunity is produced, but Sellards and Goodpasture demonstrated that this is relative only, for they successfully re-inoculated with the disease patients who had undergone a course of salvarsan treatment. Apparently, saturation of a community with yaws virus produces a relative immunity to syphilis. On these grounds may be explained the well-authenticated fact that syphilis is absent amongst the Polynesians of Fiji, Tonga and Samoa, in whom yaws is especially prevalent. Formerly Fijians were in the habit of inoculating their children against yaws to protect them from subsequent attacks. As far as accurate experiments have gone, immunity in syphilis is acquired much earlier than in yaws.

Duration and recurrences.—Yaws lasts for weeks or months or years, its duration depending on general health, idiosyncrasy, hygienic conditions, and the treatment. Mild cases in healthy subjects terminate in about six weeks; though the average duration of an attack is estimated at about one year. In other instances, especially in the debilitated, the disease runs on for months, successive crops of eruption being evolved. Sometimes these recurrences may stop short at the stage of desquamation, or at the papular stage, or they may proceed to the formation of typical yaws. They are usually preceded by feverishness, pains in the bones and joints, and the successive crops may either be limited and partial in their distribution, or general.

Sequelæ.—Contrary to general opinion, Harper in Fiji believed that late manifestations of yaws occur as in syphilis and that they produced neurological conditions resembling those of locomotor ataxia and general paralysis. Lambert recorded in the South Pacific 42 Melanesians and Polynesians who died in Samoa of G.P.I.; furthermore, aneurysmal dilatation and aortic disease were comparatively common.

Chossier, in routine post-mortems in Haiti, found aneurysms and other arterial degenerations in chronic yaws, but more recent writers (Blacklock), in assessing the clinical differentiation of yaws and syphilis, have once more remarked upon the comparative rarity of visceral and neurological lesions of the latter amongst native races. In yaws the Wassermann reaction of the cerebrospinal fluid has been generally found negative, especially in the tertiary stages. Chesterman emphasized the comparative frequency of new growths following yaws and has recorded melanoma, implanted upon crab yaws of the foot.

Mortality.—Although in the literature reference is made to deaths from yaws, yet, judging from the statistics collected by Nicholls, the mortality must be small indeed.

Diagnosis.—A painless, insensitive, larger or smaller, circular, encrusted red, granulomatous excrescence occurring in an endemic district is almost certainly yaws. The most important point about yaws, both in diagnosis and in ætiology, is its relationship to *syphilis*. Both diseases may occur in the same individual (Powell cites two cases, and Charlouis two, of syphilis supervening on yaws); and antecedent syphilis certainly does not confer absolute immunity to yaws, nor antecedent yaws to syphilis. The serum in both diseases gives a positive Wassermann reaction. Yaws may die out in a community, as in British Guiana (Daniels), yet syphilis remain; yaws may be universal in a community, as in the Fijians, Tongans and Samoans, and yet true syphilis, whether as an acquired or as a congenital disease, be unknown. In yaws, Hutchinson's famous syphilitic triad—the characteristic notched teeth, nerve deafness, and interstitial keratitis—are absent.

Table IX shows the main points of differentiation.

TABLE IX

YAWS	SYPHILIS
Not congenital.	Congenital.
Primary sore—extragenital.	*Primary sore*—usually genital.
Secondary stage	*Secondary stage*
(*a*) Typical yaw pathognomonic; furfuraceous desquamation and plantar lesions characteristic.	(*a*) Seldom imitates framboesia.
(*b*) Mucous membranes not affected.	(*b*) Mucous membranes affected.
(*c*) Itching common.	(*c*) Itching rare.
(*d*) Alopecia unknown.	(*d*) Alopecia may occur.
(*e*) Eyes unaffected.	(*e*) Iritis common; choroiditis and retinitis rare.
Tertiary stage	*Tertiary stage*
(*a*) Visceral lesions absent.	(*a*) Visceral lesions occur, e.g., pericellular cirrhosis, gumma of liver, kidney.
(*b*) Nervous system not usually affected.	(*b*) Nervous system liable to infection: tabes, G.P.I.
(*c*) C.S. fluid always negative Wassermann (Fischer; Turner, Saunders and Johnson).	(*c*) C.S. fluid usually positive Wassermann.
(*d*) Blood-vessels: no endothelial proliferation as in syphilis.	(*d*) Endarteritis obliterans of viscera —cerebral thrombosis.
Yaws better resisted. Constitutional disturbance slight; great exuberance of eruption and cheloid scarring.	Syphilis attacks constitution, affecting the vital structures.
Does not respond to mercury.	Responds well to mercury.

Secondary yaws may have to be differentiated from bromide rashes.

TREATMENT

General measures.—All are agreed on the propriety of endeavouring, by good food, tonics and occasional aperients, to improve the general health. Most are agreed on the propriety of endeavouring to procure a copious eruption by stimulating the functions of the skin—by warm demulcent drinks; by a daily warm bath with plenty of soap; and, during the outcoming of the eruption, by such diaphoretics as liquor ammoniæ acetatis and guaiacum. Warm clothing is indicated. In crab yaws a local application of 2 per cent. tartar-emetic ointment in vaseline is very useful.

I. Salvarsan, neosalvarsan (Neoarsphenamine[1]).—Except where much bone destruction has taken place, salvarsan, or better still its more recent and more soluble derivatives, has an almost magical curative effect upon yaws in every stage of the disease. The most generally used drug at the present time is neosalvarsan (neoarsphenamine). It is given intravenously to adults, and, if possible, to children; or intramuscularly (0·4 grm. dissolved in oil, into the buttock). The more urgent symptoms yield much more rapidly than do those in syphilis, and relapses are not so common. Since the introduction of salvarsan the natives of the Congo dislike being treated until the secondary rash is well out. For adults the intravenous dose advocated is 0·6–0·9 grm.; for young adults 0·6 grm., for children up to ten years of age 0·3 grm., and for children under two years, 0·1 grm.

---

[1] Throughout this account the terms arsphenamine and neoarsphenamine are given as

The systematic use of neosalvarsan in a yaws community would, if thoroughly carried out, promptly get rid of the endemic disease, and, wherever possible, it should be enforced. The average time to effect a clinical cure is eleven days. In Samoa it has been found necessary to give three injections of 0·6 grm. of neosalvarsan, at weekly intervals, for an adult male, and appropriately smaller doses for women and children. Babies are treated by intramuscular injections. Moss in San Domingo found that the cure after three injections is permanent. The great objection to mass treatment of native populations with the salvarsan compounds is their prohibitive cost. Apparently, mercury and potassium iodide have little therapeutic action in yaws of adults as compared with syphilis, but in breast-fed children these drugs will cure the infant through the mother's milk.

II. Bismuth.—The successful treatment of syphilis by Fournier with sodium-potassium-bismuth tartrate led to the adoption of a similar method in yaws. The considered opinion of workers is that none of the many bismuth preparations can be said to take the place of the synthetic arsenicals in African yaws and syphilis. The most active form appears to be the *sodium tetra-bismuth tartrate* in both secondary and tertiary yaws.

All preparations act more efficaciously when given in the early stages. Injections should be made deep into the subcutaneous fascia, and occasionally some induration and abscess-formation may result. When treating natives on a large scale, a soluble form of sodium-bismuth tartrate (*Sobita*[1]), is preferable. This was introduced by J. O. Shircore, and is now manufactured locally in East Africa. The dose is 3 gr. dissolved in 3 c.c. of distilled water, or in oil injected intramuscularly; for children up to two years, ½–1 gr; from two to eighteen years, 1–2 gr.; and for aged persons 1½–2 gr. The generally accepted dosage for an adult is 1½–4 gr. weekly with a total dosage of 6–14 gr. Children tolerate relatively larger doses than adults. Since 1924, over a million cases have been treated in Tanganyika alone by this method.

Rutter adopted sobita as the standard method of treatment in the Solomon Islands. Three consecutive injections resulted in the healing of 66 per cent. of secondary and 78 per cent. of late tertiary lesions, but relapses tended to occur within six months, though this tendency is less in the late tertiary than in the secondary stage. No significant differences could be observed between neosalvarsan and sobita during this investigation.

In patients with septic mouths, stomatitis and albuminuria are apt to ensue as a result of this bismuth treatment. Other toxic effects are diarrhœa and skin rashes, while lassitude and articular pain occur in some cases. This, and the fact that three or more injections are necessary, have been the greatest objections to the general use of bismuth,especially in the Solomon Islands and the Congo. On the whole, the toxic effects of bismuth are less frequent and are milder than those of mercury and salvarsan. In Jamaica, the dioxide of bismuth is preferred, and next in favour is the oxychloride. Bismuth salicylate is also used in 10 per cent. suspension in olive oil. In Jamaica six to ten treatments are given. In the waging of a great anti-yaws campaign, as at present in Kenya and Tanganyika Territory, bismuth has the undoubted advantage of cheapness, costing less than half a farthing a dose. According to Hanschell, stomatitis may be avoided if injection is made into the deep subcutaneous tissues, rather than intramuscularly, and the resulting pain may be mitigated.

---

[1] This preparation is placed on the market by Howard & Sons.

Bismostab (Boots) is metallic bismuth suspended in glucose solution. When given deep-subcutaneously, it is practically painless. The dosage is 20 cg. (3 gr.) locally, and a total of 6 grm. (90 gr.) can be given altogether in refractory cases. In the tropics, however, preparations of bismuth metal have been abandoned as they are apt to block the needles.

Casbis (Bayer), a sterile oily suspension of bismuth hydrate in fine dispersion, is highly spoken of on account of the fineness of the suspension. Adults receive 0·5–1 c.c. doses, and the total dosage is 12–15 c.c.

III. Combined treatment.—According to latest reports, the combined *neo-bismuth* treatment is the most effective. By combining bismuth and neosalvarsan (neoarsphenamine), in alternating weekly injections, the chances of severe reactions are reduced. Neosalvarsan is given intravenously and bismuth intramuscularly. Attempts to combine the two preparations in one compound are now being made. *Bismuth arsanilate* (Martindale) in sterules containing Bi_2O_3, 58 per cent., arsenic, 17 per cent., given by injection, has been tried in Tanganyika and Nigeria. Other preparations, known as *neotreparsenan* and *bismuth arsphenamine sulphonate*, are given in doses of 20 cg. (3 gr.) per week up to a total of 6 grm. (90 gr.). It is said that the addition of 0·1 c.c. of *butyn* exerts a local anæsthetic effect. A French preparation, which is well tolerated, is known as *Bivatol.*

IV. Arsenical preparations given by the mouth.—*Stovarsol* is a much more convenient method of mass-treatment than injections of salvarsan. It is customary to commence with 1 grm. daily, increasing to 1½, 2, and 3 grm. on successive days for adults ; ½–1 grm. for children. After a total of 8–15 grm., according to van den Branden and Lefrou, the Wassermann reaction becomes negative. Chesterman considered three courses necessary to effect a cure, but found that he could give in stovarsol ten times the corresponding dose of neosalvarsan. Slight diarrhœa is the only untoward symptom of intolerance occasionally observed, though he gave as much as 2 grm. to children at a single dose. One objection to stovarsol is that the full course may be more expensive than injections of salvarsan. *Halarsol* (May & Baker), oxyamino-phenyl-dichlorasine, in intravenous and intra-muscular injections in doses of 0·125 to 0·25 grm. for three doses at three- to four-day intervals, has been proved on the Congo to be efficacious in all stages of yaws. The minimal toxic dose is 4·5 mgm. per kilo.

Carbarsone, p-carbamino-phenyl arsonic acid, first prepared by Ehrlich, contains 28·85 per cent. of arsenic. It is given in the same doses as stovarsol and the therapeutic dose is 75 mgm. per kilo bodyweight. A number of other preparations for the treatment of yaws and tropical syphilis are detailed in Chap. 49, p. 828.

Prophylaxis resolves itself into the adoption of measures to prevent contagion. These are the isolation and segregation of the affected ; the dressing and treatment of wounds in the hitherto unaffected ; the application of antiseptic ointments to yaws sores, so as to obviate the diffusion of spirochætes by flies ; the purifying or destruction by fire of houses or huts notoriously infected ; the prevention of pollution of bathing-water by yaws discharges ; and, especially, the prompt treatment of the infected by salvarsan and bismuth.

CHAPTER XXXIII

MYCETOMA AND BLASTOMYCOSIS

Synonyms. Madura Foot ; Pseudactinomycosis.

Definition.—A fungous disease of warm climates, affecting principally the foot, occasionally the hand, rarely the internal organs or other parts of the body. It is characterized by enlargement and deformity of the part ; an oily degeneration and general fusion of the affected tissues. The disease runs a slow course, is never recovered from spontaneously, and, unless removed, terminates after many years in death from exhaustion.

History and geographical distribution.—It was first described by Kämpfer in 1712. Subsequently it was confused with tuberculous disease. Carter, from 1865 to 1874, furnished the information upon which modern descriptions are based, and since then further advances have been made by Bouffard and Brumpt.

In India, mycetoma is endemic in widely scattered districts, although whole provinces, as that of Lower Bengal, enjoy an almost complete immunity. It appears to be acquired only in rural districts, the inhabitants of the towns being exempt. Among the more afflicted districts may be mentioned Madura—hence the name " Madura foot " by which mycetoma is often known—Delhi, various places in the Punjab, Kashmir and Rajputana. In recent years we have had accounts of its occurrence with some degree of frequency in Senegambia, Somaliland, Aden, Algeria, Egypt, the Sudan, Madagascar, Cochin-China, Italy, the United States, and South America. The following varieties have been described :—

i. Actinomycotic Mycetoma

Caused by the ray-fungus, *Discomyces bovis* (Harz, 1877). Actinomycosis has a world-wide distribution and is a common disease of cattle. It destroys bone by erosion and spares only nerves and tendons. The pus from the affected region contains small yellowish granules (" sulphur grains ") of irregular shape, attaining at most 0·75 mm. in diameter. They are soft and consist of an inextricable felted mass of mycelium. The threads are radially arranged at the periphery of the grain, and their free extremity widens into a bulbous, club-like termination (10–20 μ long by 8–10 μ wide). These clubbed ends have been looked upon by several authors as forms of degeneration.

ii. Vincent's White Mycetoma

Caused by *Discomyces maduræ* (Vincent, 1894). This kind of mycetoma is common and widely distributed. It has been observed in Algeria, in Abyssinia, in Somaliland, in Cyprus, in India, in Argentina, and in Cuba.

Unlike *D. bovis* and other mycetoma-producing fungi, it does not destroy bone, and does not seem to act directly on the general health of the patient, though ultimately and indirectly it may bring about cachexia.

iii. Nicolle's White Mycetoma

Caused by *Sterigmatocystis* (*Aspergillus*) *nidulans* (Eidam, 1883). So far, only a few cases have been observed, by Nicolle and Pinoy, in Tunis, but probably it occurs in many places, the parasite *S. nidulans* being widely distributed.

Primary infection probably takes place from barley grain. The grains formed by this fungus may also attain the size of a pea, but they differ from those of *Discomyces maduræ*, inasmuch as they are more or less spherical and present a smooth surface.

iv. BOUFFARD'S BLACK MYCETOMA

Caused by *Aspergillus bouffardi* (Brumpt, 1906). The grains are quite characteristic. They are black and vary in size from a pin's head to that of No. 1 shot. They present a mulberry-like surface which is smooth and glossy, the structure consisting of a coiled-up mass.

v. CARTER'S BLACK MYCETOMA

Caused by *Madurella mycetomi* (Laveran, 1902): This mycetoma has a very wide distribution. It has been observed in Italy, in Africa (Senegal, French Sudan), and in India.

The grain formed by *Madurella mycetomi* is dark-brown or black. It measures 1 to 2 mm. in diameter, is hard and brittle ; its surface is irregular and frequently presents pointed eminences which differentiate it from the larger and smooth grains of *Aspergillus bouffardi*. The grain is composed of white threads, always over 1 μ in diameter and attaining at times 8 to 10 μ, which secrete a dark-brown substance that cements them together.

vi. BRUMPT'S WHITE MYCETOMA

Caused by *Indiella mansoni* (Brumpt, 1906). This form was described from a specimen of Indian origin in the museum of the London School of Hygiene and Tropical Medicine.

The grains peculiar to this form are hard, white, and very small, varying in size between ⅛ and ¼ mm., and having a lenticular shape. Some are bean-shaped and flat. To study their structure it is necessary to boil them first in a solution of caustic potash. The hyphal threads are large and closely set, but without any cementing substance between them. The periphery of the grain contains numerous large chlamydospores having thick walls and being full of protoplasm.

vii. REYNIER'S WHITE MYCETOMA

Caused by *Indiella reynieri* (Brumpt, 1906), originally described by Reynier from a specimen in Paris ; a second case has been recorded from Greece.

The grains may attain 1 mm. in diameter ; they are soft, white, and consist of a coiled-up strand which gives them a peculiar appearance resembling the excrement of earthworms.

viii. BOUFFARD'S WHITE MYCETOMA

Caused by *Indiella somaliensis* (Brumpt, 1906). This form is perhaps even more common in India than Vincent's white mycetoma. Bouffard has found it twice in Somaliland.

Indiella somaliensis is a most destructive fungus. In a foot examined by Brumpt all the muscles, tendons, and bones had been replaced by sclerosed tissues, more or less homogeneous, presenting numerous sinuses full of yellowish grains clustered together like fish-roe, and many small inflammatory nodules containing one or more grains. .

Culture.—Cultures can be made, as in actinomycosis, both under äerobic and anäerobic conditions on glucose or glycerol-agar plates, in shake cultures or in Loeffler's serum. Some workers recommend keeping cultures in an atmosphere of CO_2. The medium should be inoculated directly with colonies from the pus but, owing to slow growth of the actimonyces, pure cultures are somewhat difficult to obtain, unless the pus is free from contamination with other organisms.

Pathology.—On cutting into a mycetomatous foot or hand the knife passes readily through the mass, exposing a section with an oily, greasy surface, in which the anatomical elements in many places are unrecognizable, being, as it were, fused together, forming a pale, greyish-yellow mass. The bones have in parts entirely disappeared; where their remains can still be made out, the cancellated structure is very friable, thinned, opened out, and infiltrated with oléaginous material. Of all the structures, the tendons and fasciæ seem to be the most resistant.

The most remarkable feature revealed by section is a network of sinuses and communicating cyst-like cavities of various dimensions, from a mere speck to a cavity an inch or more in diameter. Sinuses and cysts are occupied by a material unlike anything else in human morbid anatomy. In the black varieties this material consists of a black or dark-brown, firm, friable substance which, in many places, stuffs the sinuses and cysts; manifestly it is from this that the black particles in the discharge are derived. In the white varieties the sinuses and cysts are also more or less stuffed with a white or yellowish roe-like substance, evidently an aggregation of particles identical with those escaping in the corresponding discharge. In the very rare red variety the colour of the accretions is red or pink.

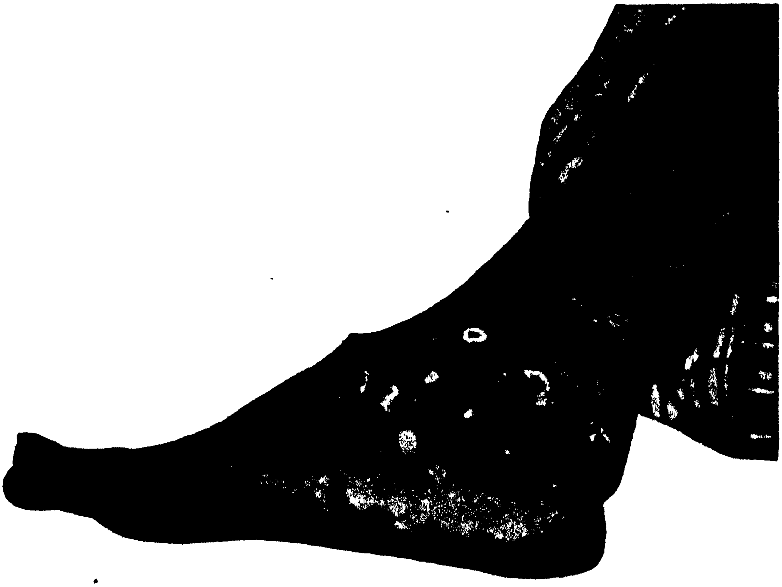


Fig. 101.—Mycetoma of about two years' standing. (*After Legrain.*)

Under the microscope the mycotic elements can be readily recognized in the concretions. In microscopic sections of the tissues, evidences of extensive degenerative changes, the result of a chronic inflammatory process, can be made out. An important feature is a sort of arteritis obliterans, or extensive proliferation of the endothelium of the arteries, and, according to Vincent, a thickenin of the adventitia of the vessels as well as of the capillaries in the more af

Symptoms.—Mycetoma begins usually, though by no means invariably, on the sole of the foot. The first indication is the slow formation of a small firm, rounded, somewhat hemispherical, slightly discoloured, painless swelling, perhaps about ½ in. in diameter. After a month or rather more, this swelling may soften and rupture, discharging a peculiar viscid, syrupy-looking, oily, slightly purulent, sometimes blood-streaked fluid holding in suspension certain minute, rounded, greyish or yellowish particles, often compared to grains of fish-roe. In other examples of the disease the particles in the discharge are black, having the size and appearance of grains of coarse gunpowder. Sometimes these particles are aggregated into larger masses up to the size of a pea. In time, additional swellings, some of which break down and form similar sinuses, appear in the neighbourhood of the first, or elsewhere about the foot (Fig. 101). The sinuses are mostly permanent, healing up only in a very few instances. Gradually, the bulk of the foot increases to perhaps two or three times its normal volume (Fig. 102). There is comparatively little lengthening, but there is a general increase in thickness, so that in time the mass comes to assume an ovoid form, the sole becoming convex, the sides rounded, and the anatomical points obliterated. The toes may be forced apart, bent upwards at the tarso-phalangeal joints, or otherwise misdirected, so that when the foot is placed on the ground the toes do not touch it. The surface of the skin is roughened by a number of larger or smaller, firmer or softer hemispherical elevations, in some of which the orifices of the numerous sinuses open.

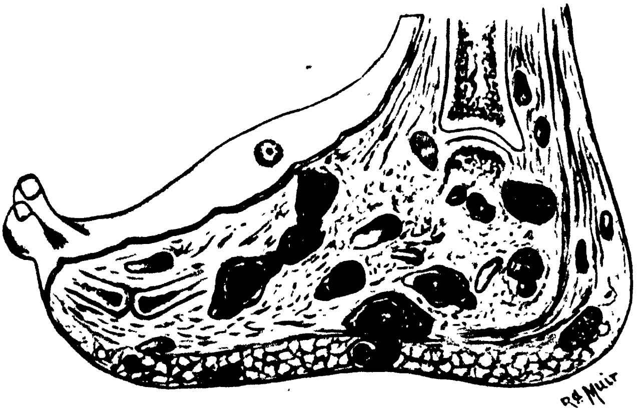


Fig. 102.—Section of a Madura foot. (*T. R. Lewis.*)

The discharge from the sinuses differs in amount in different cases, and from time to time in the same case; whether profuse or scanty, it always exhibits the same oily, mucoid, slightly purulent appearance, and may stink abominably. With a very few exceptions it contains either the grey or the black grains, rarely reddish or pink ones.

As the foot enlarges, the leg atrophies from disuse; so that in the advanced disease an enormously enlarged and mis-shapen foot, flexed or extended, is attached to an attenuated leg consisting of little more than skin and bone. In some cases the tibia or bones of the forearm are involved:

in others the disease at first may be confined to a toe, or a finger, or other limited area. In a very few instances the seat of the disease is the knee, thigh, jaw, or neck. Unless the case be one of actinomycosis, the internal organs are never implicated, either primarily or secondarily. The lymphatic glands, likewise, although they may show adenitis from secondary septic infection, are very rarely involved.

After ten or twenty years the patient dies, worn out by the continued drain, or carried off more suddenly by diarrhœa or other intercurrent disease.

Treatment.—The only effective treatment is amputation, well above the seat of the disease; for the long bones may be implicated, as well as the small bones, and unless the entire disease be removed, it will recur in the stump. Complete removal is not followed by relapse. If a toe, or a small portion of the foot or hand, is alone involved, this may be excised. Potassium iodide in large doses has been found beneficial in certain forms.

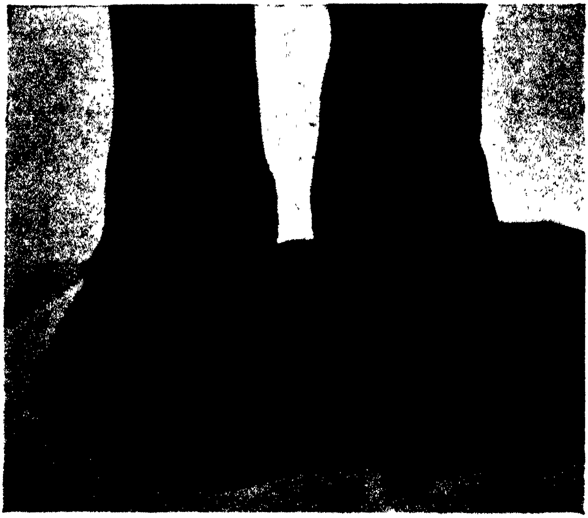


Fig. 163.—Chromoblastomycosis of feet, "Mossy foot," from British Guiana. (*Dr. Wase-Bailey.*)

Buchanan recommended surgical removal of as much diseased tissue as can be conveniently reached. Then tincture of iodine should be injected into any suspicious area remaining, in the hope that the surviving elements will be killed; therefore 1–2 c.c. of iodine should be injected every ten days for at least two months. At first, the local reaction is not severe, but later it becomes so. Probably a less irritating solution, such as Lugol's, would be better.

Potassium iodide should be given by the month in large doses over a considerable period, and there are those who think that the French tincture of iodine is more effective if administered in frequent doses of 2 drops in milk. Quite recently, the sulphonamides—sulphapyridine and sulphathiazole—in full doses have been found effective in actinomycosis of the bowel, and therefore should be given a therapeutic trial in Madura foot.

BLASTOMYCOSIS

This term is used to indicate lesions, other than mycetoma, produced by the proliferation of certain yeast-like fungi in the tissues. Normally these are either saprophytic or live as parasites on animals or plants, and appear to be especially abundant in tropical countries. Doubtless they get access to the human tissues through some wound or breach of surface. The following clinical types have been recognized:

I. Chromoblastomycosis "Mossy foot" (Fig. 103).—A papillomatous condition of the legs and feet first described by W. Thomas in the Amazon Valley, Brazil, but now reported from Honduras, North, East and South Africa, Porto Rico, Southern United States, Dutch East Indies, Japan, South Russia and Rhodesia.

The disease is due to an infection of the skin with a fungus—*Phialophora verrucosa* (Thaxter, 1915). The organism has also been named *Fonsecæa compactum* or *F. pedrosi*. The fungus can be cultured on ordinary media, and forms a blackish growth in stab cultures on ascitic agar or serum media. Chlamydospores 8–15 μ in diameter, as well as conidia, are produced and sometimes aërial hyphæ. The organisms are akin to the saprophytic moulds common on vegetation.

The foot and ankles—usually of males engaged in agriculture—are covered with warty outgrowths resembling barnacles, which are vascular and sometimes painful. They are usually papillomatous, but occasionally pedunculated. The sole of the foot usually escapes. It is claimed that the disease can be inoculated into the nose of rabbits producing a verrucoid mass.

The diagnosis is established by demonstration in sections of a tuberculoid type of reaction with rounded brown bodies resembling yeast cells (Simpson, Harington and Barnetson, 1943). The best treatment is actual cautery.

II. Coccidioidomycosis.—Cutaneous patches, of various dimensions, of small warty excrescences with minute abscesses or encrusted ulcers, especially at the periphery of the patch.

Coccidioidal granuloma, or Posada's Disease (Rexford and Gilchrist, 1894) was first discovered in Buenos Aires by Wernicke in 1892. It has been found especially in Brazilians, in whom it causes extensive ulceration. The pus from the lesions is easily inoculated into animals, especially guinea-pigs, in which it causes a virulent infection. Up to 1935, 400 cases had been reported, usually in Upper California, and it has also been seen in oxen, but in them produces no symptoms. It has also been found in rodents, dogs and sheep, in Arizona, Texas, Old and New Mexico. Infection is probably caused by inhalation of the spores, and the skin lesions originate round the site of scratches and other lesions.

Another form, "valley fever" or "desert fever" of the San Joaquin Valley, resembling erythema nodosum with pulmonary involvement and easmophilia, is probably a generalized infection from inhalation of chlamydospores. The affected skin patches may remain pigmented. The disease usually presents an influenza-like initial phase. Arthritis and phlyctenular conjunctivitis have been noted. Sensitivity is established within fourteen days and an intradermal test with "coccidioidin" is now employed. An epidemic in San Benito County has been reported by Davis and Smith, and it has been shown that 80 per cent. of persons who have lived in the S. Joaquin Valley for over ten years are sensitive, and also Indian children in the reservation.

The organism is *Coccidioides immitis*. The cells occur either isolated or in giant cells. They are spherical and thick-walled, with a diameter of 2–80 μ. The organism reproduces by endospore formation ; budding is absent. The wall of the ascus often shows radiate formation. On all the usual media the colonies are flat and greyish, becoming white to light cream, with aërial hyphæ, which in microscopical appearance are septate, branching, hyphal swellings ; arthrospores measure 2·5–7 μ in diameter ; chlamydospores are abundant, 5–8 μ in diameter. Studies in metabolism of *C. immitis* show that the organism is resistant to desiccation, but the chlamydospore develops under conditions of drying, and it is impossible to infect animals in the absence of this spore. This resistance to drying is an important factor in dissemination of the organism in California. *C. immitis* has been isolated from the desert soil by Stewart, Meyer, Emmons and Ashburn. Pochet mice (gophers) and kangaroo rats form a natural reservoir of the disease.

The cutaneous type of blastomycosis also includes the following conditions :

North American Blastomycosis or Gilchrist's Disease (1894) (*Zymonema dermatitidis*).—An infectious granuloma, acute or chronic, with cutaneous or systemic lesions—papulo-ulcerative, verrucous, or papillomatous, or gummatous, showing typical violet colour. The organism has simple or budding yeast-like cells, thick-walled, 5–20 μ in diameter ; the colonies on culture are yeast-like. Hyphæ are septate and branching, 2–4 μ in diameter ; conidia are pyriform or round, 5 μ in diameter.

European Blastomycosis (*Cryptococcus hominis*) is clinically similar to Gilchrist's disease, but ulceration is common in the cutaneous form, with abscesses, and it quite commonly invades the cerebro-spinal system. The organism has thick-walled, heavily-encapsuled, simple or budding cells, 5–10 μ in diameter. Colonies on culture are "yeasty," smooth, mucoid or moist, and spherical or ovoid with budding encapsulated cells approximately 2–6 μ in diameter.

South American Blastomycosis, or Splendore de Almeida Disease (Lutz, 1908) (*Paracoccidioides brasiliensis*), is generalized or localized, cutaneous or systemic, the lesions being granulomatous, papular, verrucous or ulcerative. It spreads by the lymphatics. The cells are spherical or ovoid, 1–30 μ in diameter, rarely larger, with thick walls.

III. Lingua nigra.—A form occurs on the tongue, leading to hypertrophy of the filiform papillæ, and causing a condition known as *lingua nigra*. The organism is known as the *Cryptococcus linguæpilosæ* ; it has a double contour, is composed of oval yeast-like cells and mycelia elements, and can be cultivated on maltose-agar. Wilkinson (1940) and others claim that *lingua nigra* can be cured by nicotinic acid.

IV. Pulmonary Blastomycosis.—*Cryptococcus capsulatus*, allied to *C. farciminosus* of the horse, has been demonstrated in the epithelial cells of the lung by Darling, who named it *Histoplasma capsulatum*. The disease it produces in many respects resembles kala-azar, and is accompanied by splenomegaly, anæmia, irregular pyrexia, and leucopenia (*see* p. 853).

Niño in Argentina has described, as *Cryptococcus pyschrophylicus*, an organism which caused a generalized infection originating from an ulcerated condition of the face. The organism grew best at 22–25° C., but was arrested at 37° C. Guinea-pigs, white mice, and rats were susceptible to inoculation.

V. Sporotrichosis.—This has been reported from Southern France, Southern U.S.A., South America, and South Africa, where it is common amongst the miners of Witwatersrand. It produces gumma-like swellings in limbs or trunk, which enlarge and ultimately break down, leaving deep ulcers, due to organisms, *Sporotrichum* (*Rhinocladium*) *beurmanni*, or *S. schenckii*, which usually exist saprophytically, and gain entrance to the body through an abrasion of the skin or œsophagus. Occasionally they may be demonstrated in the blood; the lymphatics, eye, oral cavity, periosteum, muscles, or viscera may become involved. In the discharges and tissues the parasites are scanty, so that the mycotic nature of the disease can only be made out from cultures. Benham and Kesten isolated the organism from linear nodules in the arm, and reproduced the lymphatic type of infection in a monkey. Inoculation of white rats produced typical orchitis. In man infection may be caused by a thorn prick or other injury.

Pijper and Pullinger (1927) recorded 14 cases in native miners on the South African Rand. They distinguished a primary sore in the form of a localized ulceration on a finger, or the shin. Ten of the fourteen cases had the lesions confined to one arm; the others were on the shin, with lesions extending up as high as the buttock. Incision of the nodules in the paths of the lymphatics produced pus or serous fluid.

Sporotrichum beurmanni can be isolated from the tissues by aspiration and insemination on to Sabouraud's medium. The parasite occurs in wild rats in Argentina and Brazil, while a similar disease, apt to be mistaken for epizoötic lymphangitis, occurs in horses and mules in Madagascar (Carougeau).

It appears to be a common parasite in nature, and recently (1933) Benham and Kesten have transmitted the human parasite to carnations, in which it produces a "bud rot" similar to that caused by a natural parasite, *S. poæ*.

The parasitic elements are very scanty in the pus, and in mycelial elements are seen either in sections or in cultures. Individual cigar-shaped yeast-like parasitic elements are often found engulfed by phagocytes.

Hemisporosis (*Hemispora stellata*) is a disease like sporotrichosis reported from Italy, and is characterized by granulomatous growths resembling syphilis or tuberculosis. Occasionally bones are affected.

VI. Torulosis.—This gives rise to grave lesions of the pulmonary and nervous systems, and local tumours of a peculiar consistency containing round cells surrounded by a gelatinous substance secreted by the organism. It is found especially in California. The parasite, which has been especially studied by Kessel, is known as *Torulopsis histolytica* (Stoddard and Cutler, 1916), synonym, *Cryptococcus histolyticus*. The yeast-like cells are usually found in the cerebro-spinal fluid. Experimental infections are easily produced in rats and mice by intraperitoneal injection, generalized lesions being found in lungs, liver, spleen, kidneys and brain. Kessel and Holtzwart found 45 cases reported; most have involved the central nervous system and four have exhibited general infection. In four other cases infection was localized to the muscles of the vertebral column, to pelvic and inguinal abscesses, or to the tongue or nasopharynx. In one case from Los Angeles lesions were confined to the knee. This disease appears to be incurable. The diagnosis is usually made by cerebrospinal puncture. The protein content and globulins are raised, as in other forms of meningitis; the sugar content is lowered and chlorides reduced.

T. histolytica is a primitive form of yeast cell; it multiplies by gemmation, does not produce endospores or mycelium, and can be cultured in glucose broth or on Sabouraud's medium. The colonies are glistening white, and show no mycelia penetrating into the substratum, as is characteristic of Monilia. The individual cells multiply by gemmation, no hyphæ being observed. The cells exhibit characteristic capsules. No asci are formed.

The sugar reactions are typical: no acid or gas is produced in arabinose, dextrose, galactose, inulin, maltose, mannitol, raffinose, sucrose, lactose or dextrin. The reaction in milk is alkaline. When it is inoculated intraperitoneally into rats and mice, the animals die in eight to twenty-eight days, and the organisms can be recovered from the tissues. Monkeys inoculated intracardially develop small nodules on the face, eyelids and ears, cutaneous lesions containing the organism. In some monkeys, however, a general torulosis of the brain and spinal cord develops.

Diagnosis.—Usually the lesions of blastomycosis in the first instance suggest syphilis or tuberculosis. Specific treatment and absence of reaction to tuberculin and of the tubercle bacillus should lead to a careful search for yeast-like organisms in the discharges or scrapings. Widal and Abrami found that the serum of sporotrichosis will agglutinate cultures of the specific organisms; while Malvoy and Ricketts have demonstrated a complement-fixation test in blastomycosis, using an old culture as an antigen. Martin (1935), especially, employed this method in diagnosis. The antigen was a suspension in salt solution of the organisms grown at 37° C. on beef-infusion, at *p*H 7·4, on blood-agar slants. The patient's serum was inactivated at 56° C. for fifteen minutes, and the test was carried out as for the Wassermann.

Treatment.—All forms of blastomycosis are exceedingly chronic and resistant to treatment. Surgical measures are useless, but large doses of the iodide of potassium or of sodium (20–30 gr. three times a day, well diluted) are sometimes effective, and should always be tried and, if found beneficial, continued until cure is well established. In sporotrichosis the tumours can be punctured and injected with potassium iodide, 1 in 100, while treatment must be continued for some time after apparent cure. X-rays are at times a useful adjunct. *Coccidioides immitis* is said to be amenable to sulphonamide therapy.

Section V.—DISEASES OF THE CENTRAL NERVOUS SYSTEM

CHAPTER XXXIV

NEURASTHENIA IN THE TROPICS

PSYCHONEUROSES play a considerable part in adding to the burdens of life, and are the cause of a proportion of invaliding among European officials and business men from the tropics ; more especially from West Africa. As a cause of disability, neurasthenia or anxiety psychoneurosis, or whatever term may be applied to this real and distressing condition, has superseded tropical diseases. Therefore, from the point of view of Colonial Administration, neurasthenia is of greater importance than the majority of the tropical diseases with which this book deals. There is nothing peculiar to tropical neurasthenia which differentiates it from similar anxiety neuroses in temperate climates.

When it is considered that, in the figures quoted by Squires, no less than 45 per cent. of 358 invalidings of Europeans from the tropics were for psychological reasons, there is obviously some feature in life under tropical conditions which pre-disposes towards this state. Fully developed and frank neurasthenia, as seen in its most characteristic form, is more apt to develop in a neurotically-disposed individual than in one of a complacent and unemotional mental make-up, and it is not always possible to gauge with accuracy those individuals in whom tropical neurasthenia will eventually develop. Culpin pointed out that certain persons go to the tropics as a flight from the strain of social life at home.

In an analysis of neurasthenia in West Africa Rowland Hill (1943) found that patients with long-standing conditions of nervous instability were made worse by tropical life, but in nearly all there was evidence that the neurasthenic tendency had been exaggerated by disease acquired in the tropics.

***The influence of tropical infections* (p. 15).—Tropical infections, especially the enervating, debilitating, and irritating recurrent relapses of malaria, are predisposing factors. The recurrent headaches and fevers encourage patients to refer sensations to the cranium, so that they complain of neurasthenic headache, lack of concentration, loss of memory (West Coast Memory), and general disinterestedness in life. Intestinal infections, such as amœbic or bacillary dysentery, may promote concentration of thought on the intestinal tract. The patient's attention becomes rivetted on his digestive system, with the result that introspective psychoneurosis develops. In this respect tropical infections do undoubtedly predispose to "tropical neurasthenia." But there are other aspects of life in the tropics which engender introspection. The heat, insect life, the proximity to natives who cause annoyance and whose ways and psychology the European cannot understand, the dull monotony, the ever-recurring twelve hours of daylight alternating with twelve hours of pitchy night, and the abundant**

and vexatious insect life; all act as stimuli which goad to the neurasthenic state. The dulling of the appetite engendered by heat, the unpalatable and unsuitable food, the greasy cooking, the abundance of starchy matter, the monotony of tinned foodstuffs, together with the comparative absence of essential vitamins, all tend to upset the digestive apparatus and to depress the higher psychical centres.

Fear of disease and hypochondriasis are sources of neurasthenia in previously healthy and well-balanced people who, after serving in the tropics for long periods, have suffered a good deal of illness without much deterioration, but with loss of confidence in their ability to stand tropical life. All those who have a tendency to anxiety neurosis are made worse by exposure to heat.

Sleep.—Insomnia, which appears to be the outward manifestation of physical exhaustion and which nearly always appears towards the end of the tour in tropical Africa, is usually the first manifestation of the neurasthenic state, and imperatively indicates invaliding to a temperate climate.

Sexual factors.—Other factors will occur to anyone who has lived in isolation under tropical conditions. There is the sex factor, which may be potent; there is the social isolation which operates in out-stations; in others it is excess of alcohol, late hours, or living an unaccustomed life attended by native servants—all these may upset the mental equilibrium. Then there is, too, the constant restraint and watchfulness required to avoid offending against local prejudices, and having to live with others who are also in a state of constant exasperation.

Work and exercise.—Probably hard mental and physical work, in moderation, act as a bar rather than as a predisposing factor in the development of neurasthenia. Mental occupation tends to divert the mind from self-interest. On the other hand, mental pressure or undue stress appears to be less easily tolerated in the tropics than at home. Neurasthenia is not a special affliction of Europeans, for it is frequently observed amongst the educated native officials in West Africa, Malaya and India, though the proportion is by no means so great as in Europeans.

Neurasthenia in women.—It is difficult to state the sex incidence of neurasthenics; probably women, with their more highly developed emotional centres, are more apt to develop it, granted equal opportunities, than men.

A tropical climate usually produces certain psychological effects in women. Those who become neurasthenic suffer from pelvic pain and discomfort, menorrhagia and toxæmia. Constipation, by favouring pelvic congestion and inflammation, and uterine displacements, have also to be considered.

The effect of the tropical climate on the newly-arrived European woman is at first distinctly exhilarating. The appetite is increased and the heat does not oppress her at first as it does in succeeding years, and she has a feeling of well-being. Menstruation frequently stops for a season. The sense of well-being may be so real that risks are taken which more experienced residents avoid, such as eating unsuitable food. The long hours that European women spend in shaded houses during the heat of the day engender a feeling of lethargy, due to extra work thrown on the liver, and want of exercise.

Childbirth in European women in the tropics is apt to be more difficult and laborious than in temperate climates, due very probably to the conditions of life; but even among native women between 30 and 40 per cent. of deaths are directly or indirectly connected with parturition. Native women, as a rule, give birth with extraordinary ease, and only where they have departed from a natural mode of life, and are living in seclusion, is parturition difficult.

The effect of tropical conditions.—Tropical life may have a disturbing effect on the mentality of even the most healthy and balanced individual. After a year or more of constant exposure to heat and humidity, the hours of sleep become disturbed, and the nervous system more sensitive to external stimuli. Insomnia may be precipitated by certain electrical conditions of the atmosphere, at present little understood, skin conditions, especially prickly heat, and possibly a hyperglycæmia which Dutch investigators in Java ascribe to the climate. Otherwise healthy adults often appear "nervy" and "excitable," showing exaggerated reflexes and nervous twitchings of the face and limbs, with increased reflexes, directly they return to a temperate climate. In the minor states of disturbance the fears and stresses disappear the moment cool headwinds are encountered, and peaceful and refreshing sleep is enjoyed once more. But transference to his home climate does not immediately relieve a fully-developed neurasthenic of his fears; on the contrary, the hum and bustle around him act as further stimuli.

The effect of quinine.—In certain individuals the constant absorption of prophylactic quinine has a depressing effect. It may be a direct mental depressant; on the other hand, it may act indirectly by causing indigestion and abdominal discomfort. This subject has been discussed on p. 115, and it is open to question whether more harm, in the neurasthenic sense, is not done to some people by constant quinine, than is counterbalanced by such protection as the practice affords.

Symptoms.—The very appearance of the individual betrays his mental state. He (or she) is emotional to a degree, so that any sympathetic reference to health may provoke a flood of tears. There are others in whom the most profound depression reigns, and who may display suicidal tendencies; these are usually associated with intractable insomnia.

The patient usually complains of a headache confined to the temporal or parietal portion of the cranium. There is a sense of increased intracranial pressure. Others experience a sinking feeling in the abdomen, or indefinite abdominal pain, or flatulent dyspepsia. There is usually a mild tachycardia, or rather vasomotor instability, with a fall in blood-pressure and a diastolic pressure below 80. The reflexes are usually exaggerated, and there may be a false ankle-clonus with hyperidrosis of the palms of the hands and of the feet.

It has been suggested that the main symptoms are to be ascribed to hyperthyroidism, but the Editor has been unable to find any evidence for this hypothesis. With this degree of nervous instability it is not surprising to find divergence of the pupils on accommodation (Mœbius' sign) which by some is considered to indicate hyperthyroidism.

Treatment.—The main principle in treatment is to remove the patient from his immediate surroundings to a temperate climate with congenial companions. Usually, on arriving in a cool climate, natural sleep sets in and fears and anxieties disappear. The neurasthenic state may be temporary. On the other hand, the emotional and depressive states should be treated seriously and efforts should be made to discover some underlying infection. The Editor has on several occasions seen profound neurasthenic symptoms disappear after treatment of an underlying unsuspected malaria. If alcohol has been taken in excessive amount, it must be cut down, or prohibited altogether. Efforts should be made to divert the patient's attention from himself. Hobbies of all kinds should be encouraged and there is probably no occupation more restful and curative than fishing in Scotland or Ireland.

For insomnia, mild hypnotics should be prescribed, such as allonal, luminal, or medinal. Sleep may be induced by a hot bath or a cup of Ovaltine. As a general sedative a mixture of the following type may be prescribed, to be taken three times daily:

Ammon. brom.	gr.x (0·648 grm.)
Spirit. ammon. aromat.	♏xv (0·888 c.c.)
Syrup. aurant.	ʒi (3·55 c.c.)
Aq. menth. pip. ad	℥ss (14·21 c.c.)

℥ss three times a day after meals.

Prophylaxis.—As the main treatment of neurasthenia entails removal from immediate surroundings, its prevention is difficult. Once marked neurasthenia has developed in a European in the tropics, he should be invalided to a temperate climate and his return becomes a matter for anxious consideration. There are cases in which the patient quickly regains his mental equilibrium; but should the mental depression continue, in spite of the simple methods recommended, then permanent invaliding should be considered. The Editor is of opinion that a patient with well-marked tropical neurasthenia should never be permitted to return, otherwise the old symptoms will reassert themselves directly he arrives in his old haunts, so that after a few months he will be sent home again.

CHAPTER XXXV

ENCEPHALITIS JAPONICA

Synonym. Japanese Type B encephalitis.

Encephalitis japonica is, strictly speaking, an epidemic encephalomyelitis involving the brain and spinal cord, and is to be distinguished from epidemic encephalitis (encephalitis lethargica) by the absence of eye lesions and other features to be detailed later.

Epidemiology and geographical distribution.—Encephalitis japonica, as its name implies, is well known in Japan, where it apparently has occurred in epidemic waves since 1871. In 1933 it was found in different portions of North America (St. Louis ; Toledo ; Kansas City ; Paris, Ill. ; and St. Joseph, Mo.). In 1938 it was recognized by Pette as occurring in Germany and by Silbermann in Vienna. In 1928 Kaneko and Aoki made an intimate study of the disease and were able to differentiate it from encephalitis lethargica and to determine its identity with *Encephalitis B.* In 1924 a very severe epidemic occurred in Japan during a very hot and dry summer season, when 7,000 cases were recorded, with a mortality of nearly 60 per cent. This disease spreads rapidly, in a manner more nearly resembling poliomyelitis, more commonly and more severely attacking those over fifty years of age, in contrast to the relatively mild disease it produces in young people.

During recent years it has also appeared in China, and in the summer of 1938 there was an epidemic in Peking. Most of the cases occurred in children.

Ætiology.—Knowledge of the virus of epidemic encephalo-myelitis comes from Kobayashi, Takaki, Nishibe and Hayashi. Credit is due especially to the latter for his important researches on its transference to monkeys, in which it produces the same histopathological lesions as in man. In America, however, white mice have been found more susceptible than monkeys. Webster and Fite demonstrated that the virus, which is active in the blood and in the central nervous system in the early stages, can be inactivated by convalescent serum.

The transference of the virus from man to man has not been ascertained with certainty, but it has been suggested in China that it is transmitted by mosquitoes, mainly because it is most prevalent during the warmer months when those insects abound. There is also an analogy with equine encephalo-myelitis, which has been observed in horses as well as in man and which is transmitted in this way. Perdrau, by using hyperimmune sera, was able to demonstrate antigenic relationship between the virus of encephalitis japonica and that of St. Louis. The dimensions of the virus particles are estimated as between 20 and 30 $m\mu$.

Symptomatology.—The prodromal symptoms commonly encountered are headache, dizziness, sluggishness, and vomiting. These are followed by psychical disturbances, very often by delusions, but in very severe cases coma ensues, ending in death. The psychical signs and symptoms may be entirely absent in the mild cases, and (in contrast with encephalitis lethargica) meningeal symptoms may predominate. Disturbances of the motor system are characteristic : there are clonic contractions of the muscles which may end in actual convulsions. Fine tremors of individual groups of muscles alternate with attacks of shivering and athetoid movements. The whole muscular tone is increased in the extremities and in the neck and face, especially the masseter muscles, which results in an anxious expression, and ends in trismus making mastication impossible. In very advanced cases, encephalo-myelitis causes paralysis of the spinal cord, but, in direct contrast to encephalitis lethargica, eye symptoms are absent; nor is post-encephalitic Parkinsonianism ever observed, though bulbar symptoms, resulting in failure of speech and difficulty in swallowing, are quite common and, in addition, defects in co-ordination and sometimes even cerebellar disturbances. Anomalies of superficial and deep tendon reflexes are usually present, especially in *spastic* cases. Salivation and excessive sweating are absent.

The foregoing description covers only the main features, however; actually the clinical picture is a many-sided one. There is also another aspect to this disease in that, though the neurological side dominates the picture, there is a secondary affection of the hæmopoietic organs, resulting in a secondary anæmia, which appears to indicate a generalized infection, rather than a local affection of the central nervous system. As a rule, the temperature chart is not characteristic, and the course is afebrile. There are cases, however, in which fever is noted for five to ten days, and these are followed by sequelæ, such as profound neurasthenia. The fulminating cases, which are fatal in twenty-four to forty-eight hours, are generally pyrexial. It is to be noted that there are no pupillary or eye symptoms, and there is no special affection of the bladder or bowels. Usually there is retention at first, followed by incontinence.

Diagnosis.—The main points in differentiation from encephalitis lethargica have been noted. The cerebro-spinal fluid shows all grades of inflammatory disturbance. Kaneko and Aoki have shown that there is an increase of the albumin content from 9 to 350 mgm. per cent. Differential diagnosis has to be made from lymphocytic choriomeningitis.

Pathology.—Epidemic encephalo-myelitis is characterized by diffuse lesions in the brain and spinal cord: these take the form of small white knob-like aggregations of cells, composed of microglia intermingled with lymphocytes and leucocytes. Here and there ganglia cells are also found acutely damaged.

Treatment.—No specific treatment is at present known.

TICK-BORNE ENCEPHALITIS

A somewhat similar, widespread and fatal form of encephalitis has been described and investigated by Pawlowky and his Russian colleagues in Mongolia and Far Eastern territories in the scrubby wastes (Taiga country). This disease has distinct seasonal incidence, and 80 per cent. of cases occur in May and June.

Ætiology.—This form of encephalitis has been shown to be due to a filterable virus transmitted by the bite of a tick (*Ixodes persulcatus*), in which the virus persists, as it is found infective in wild districts uninhabited by man. The virus has been isolated from the brains of various species of wild animals indigenous to the country; these therefore constitute a reservoir of infection. Seasonal incidence of the disease during May and June corresponds with maximum prevalence of *Ixodes persulcatus*. The infection transmitted by bite of the tick is hereditary and therefore larvæ and nymphs are also infective.

Symptomatology.—This form of encephalitis has an abrupt onset and runs a severe course with steep rise of temperature, severe headache, and vomiting. Symptoms of meningeal involvement are followed by signs of focal lesions in the central nervous system, paresis and paralysis of upper or lower limbs or muscles of the neck or back. Parkinsonism never occurs. The case mortality is about 30 per cent.

CHAPTER XXXVI

LÂTAH, RUNNING ÂMOK AND KORO

Latah, a word signifying " nervous " or " ticklish," is not uncommon in the natives of the Malay Peninsula, Java, and the neighbouring islands. It occurs more frequently in women, especially young women, than in men ; children are seldom affected ; it rarely appears before puberty and is especially common at the menopause.

A somewhat similar affliction is described among the Ainu people, usually in women, and is known as *imu*. This manifests as psycho-motor attacks precipitated by some emotional shock. If a sufferer is startled, she may continue to echo everything that is said to her.

Lâtah persists for years. The main characteristics of this state are the same, though there is considerable variety in the intensity of the symptoms. The condition is incurable, shows no tendency to become worse, and does not terminate in insanity.

As the Malays say, an *orang lâtah* never becomes an *orang gila* (âmok). The subjects of " lâtah " at first appear to differ in no way from their neighbours and relations, but on some sudden and striking impression, such as a loud sound, or in response to some overt suggestion by word or deed, they pass into a peculiar mental state in which they involuntarily utter certain sounds and execute certain movements. In other instances they will imitate words or movements, or yield to suggestions from others. During this hypnotic-like state, which may last for a few minutes or longer, the victim is at the mercy of his prompter and will unerringly follow any lead indicated. Although the manifestations of high degrees of lâtah may be followed by exhaustion, or even by swooning, as a rule nothing of the kind occurs. The infirmity is usually discovered by accident. Swettenham, for instance, used to relate that it was only necessary for anyone to attract the attention of these men by the simplest means, such as holding up a finger, or calling them by name in a pointed way, touching them, or looking them steadfastly in the face, in order to make them lose control of themselves and be willing to execute whatever was suggested by a sign. On one occasion, one of them, on being told that a roll of matting was his wife, embraced it with every sign of affection ; but when the other lâtah subject, a policeman, was convinced that the same roll was his wife likewise, he too embraced it, and the two men fell to the ground struggling for the possession of the " lady."

Lâtah folk are favourite subjects for the practical joker, and in a few instances they very much object to being made a show of, and may become dangerous. Lâtah seems to be akin to certain emotional stresses which are common in all barbarous and semi-civilized countries.

Abraham has seen the afflicted, if suddenly startled, fall down and imitate the gestures of anyone in sight ; for instance, an old lady startled by a bicycle bell, will instantly imitate the pedalling of the cyclist till exhausted.

Unless unforeseen accidents occur, lâtah is not fatal. Gimlette and others have called attention to the medico-legal aspects of the disease. Fortunately, examples in which lâtah has been shown to play a part in crime are rare. Temperamentally, all the Malay races are very highly strung and nervous, although externally impassive, and there appears to be an hereditary tendency to the lâtah state in every Malay.

Young-dah-hte is a state closely related to lâtah. Mongolian races are predisposed. Heredity does not seem to play any part. It differs from lâtah in that the patient continuously remains in the imitative condition and is always liable to reactions.

Nat-win-de is a religious dance with closed eyes and swinging movements. It is started by professionals and taken up by others.

There appears to be a somewhat similar affection amongst the Samoyedes which is known as "Ikota," and it is believed that the curious epidemics of religious ecstasy, which swept over Europe during the Middle Ages, were of similar origin.

Banga is a hysterical affliction in Congo women at puberty. The subject is convulsed and rushes about uttering wild cries.

"**Âmok**" (or running âmok) is a term used somewhat loosely for a condition which, in the fully developed form, drives its victims to blind fury and to kill without reason.

Usually the "âmok" runner (or âmoker) has a grievance upon which he allows himself to brood, and after a period of sullenness decides to kill the suspected person and at the same time to destroy as many other people as possible. He therefore arms himself, runs "âmok," and buries his *kris*, when out to slay, in friend and foe alike, with the expectation of being killed in turn.

In other cases there may be premonitory signs in which a person mutters and has delusions. Quite suddenly he will run "âmok" and after the attack may fall into a deep slumber and become comatose. The liability to "âmok" attacks is greatest in the Malays and their drugs, such as Indian hemp (*Cannabis indica*), are known to be potent predisposing causes of the attack. Van Loon found that in Java "âmok" runners are often suffering from some infectious disease, and that the symptoms are hallucinations and confusion; such patients are impelled to flight and attack as reactions to imaginary dangers and the agony and terror caused thereby.

"**Koro**" occurs amongst the Macassars and the Buginese in Celebes, and is also well known among the Chinese as *Shook Jong*, originally described by Blonk in 1895. The term signifies "shrivelling," and a feeling occurs at regular intervals of the penis retracting into the abdomen; if help is not forthcoming the patient dies. In his anxiety, the patient grasps the penis, and if unable to do so, obtains assistance from others. It may be days before the attack subsides, and the sufferer cannot bear to be left alone. If help be not to hand, he will actually tie the penis to his leg with string, anchor it by means of a pin, or may even employ a double-bladed clasping instrument known as *li teng kok*, which is used by jewellers. By the native this tendency is regarded as the "Yin" principle, representing the female power, dominating the "Yang" principle, which represents the male element. In order that a "Yin" disease may be cured, a "Yang" medicine must be employed. The sufferers are generally neurotics, and the anxiety arises out of sexual conflicts. Various pathological conditions, such as œdema of the lower abdomen, hernia, hydrocele and elephantiasis of the scrotum, may evoke fear of an attack. An analogous state, characterized by diminution of the genital labia and shrinkage of the breasts, is known to occur in

Section VI.—TROPICAL VENEREAL DISEASES

CHAPTER XXXVII

LYMPHOGRANULOMA VENEREUM

Synonyms. Climatic bubo; Lymphopathia venereum; Esthiomène; Lymphogranuloma inguinale; Inguinal poradenitis; Poradenolymphitis; Nicholas-Favre disease (French).

Definition.—A type of adenitis of venereal origin, of which the primary lesion occurs on the prepuce or male genitalia. The infection—a filterable virus—causes inflammation and, subsequently suppuration of the inguinal glands. This suppurative state is usually attended by pyrexia and general constitutional disturbance. The bubonic stage occurs in the male, and some think that a general lymphœdema with ulceration, known as esthiomène, represents the analogue in the female. Most authorities also consider that the genito-ano-rectal syndrome and inflammatory stricture of the rectum are due to the same cause.

Epidemiology and geographical distribution.—Scheube originally applied the term "climatic bubo" to a type of adenitis terminating in suppuration, not uncommon in tropical countries. Whether it is becoming increasingly frequent, or whether because attention has been drawn to its peculiar nature in recent years is a moot point, but recently "lymphogranuloma" has emerged from the obscure recesses of textbooks on tropical medicine into the full limelight of general medicine, so as to merit the title of the "*Sixth Venereal Disease*," which has been bestowed upon it by Stannus.

In tropical practice it is especially prevalent amongst the European crews of warships visiting the coasts of East and West Africa, and is almost equally common in seafaring people (lascars, stewards, and British sailors) throughout the whole of India, China, Malaya, Japan, the Mediterranean, West Indies, and South America.

In 1913, Durand, Nicolas, and Favre described it in France, and possibly the condition long known as the "strumous bubo" is the same.

In 1933 Stannus and Findlay described an indigenous case in England. Since then the Editor has seen several, and more recently Anwyl Davies discovered three more. Now numerous reports of its occurrence in Italy, Rumania, and in fact the whole of Europe, are to hand. In the United States, this disease in all its phases has been discovered, chiefly in negroes. At certain times and places it appears almost to be epidemic. There seems to be no doubt, that, in almost every instance, infection is acquired by sexual intercourse.

Ætiology.—Hellerström and Wassén (1930) originally transmitted the virus obtained from the pus of inguinal buboes to monkeys, intracerebral inoculation producing meningo-encephalitis. The virus, which is apparently contained in the leucocytes, consists of minute particles which can be easily seen, and were figured by Findlay (1939). They can be stained by Victoria blue, Giemsa or Castenêda's method; with Giemsa, the larger bodies take on a bluish-purple tint, while with Castanêda's stain they are reddish-purple. Larger and smaller forms of the virus particles can be demonstrated outside the cells, lying close to cell débris, in compact colony-like masses. When they are within cells the elementary bodies may be found in the cytoplasm of either mononuclear or polymorphonuclear leucocytes. Occasionally, these groups may attain considerable size, forming cyst-like spaces; later, the cyst-wall may rupture. The larger forms have been observed in considerable numbers, chiefly within twenty-four hours of intracerebral inoculation. There therefore appears to be a development cycle of the virus which is complete in forty-eight hours. The virus particles, or granules, were first described in cells from inguinal buboes by Gay and Prieto in 1927, and similar bodies were found by Findlay in 1933. Miyagawa (1938) finally concluded that they represented the virus and gave their measurements as 0·125–0·175 μ, while Findlay, Mackenzie and MacCallum thought that they resemble similar bodies found in psittacosis by Bedson and Bland in 1932.

Intraglandular injection of guinea-pigs with the virus produces an inguinal bubo in almost every case, so that this method may be employed for diagnosis. The most reliable method at present is Findlay's intracerebral inoculation of white mice, which produces encephalitis. Miyagawa found that a chipmunk, *Tamias asiaticus*, is highly susceptible to intratesticular and intracerebral inoculation. The virus can also be cultivated on chick chorio-allantoic membrane in tissue culture. Ravaut, Levaditi, Lambling, and Cachera devised a method of isolating the virus from ulcerative proctitis by inserting a portion of tissue under the skin of a guinea-pig. After a few days, the inguinal gland is excised, emulsified and injected intracerebrally into a monkey. In inoculated mice a characteristic train of symptoms is evolved in five to seventy days, in which weakness, paresis, opisthotonos and convulsions occur. The concentration of the virus in the injected mouse brain is not great, so that dilutions greater than 1 in 1,000 fail to give positive results.

A protection test has been devised, by mixing equal parts of serum of the lymphogranuloma patient with an emulsion of infected mouse brain, diluted 1 in 5 in normal saline, and kept for the night in the ice-chest at 4° C. Doses of 0·5 c.c. injected intracerebrally do not produce encephalitis. The serum of monkeys which have recovered gives the same reaction.

Pathology.—The essential features of the pathology of the human gland consists in little pin-point epithelioid formations scattered all through the gland substance. They are made up of masses of irregularly disposed macrophage cells together with some giant cells. Höppli described localized collections of eosinophils. Subsequently tiny micro-abscesses form.

Symptoms. *Primary sore.*—Durand in 1918, and subsequently Hanschell, described a small herpetiform ulcer on the prépuce which heals in a few days; the adentitis proper does not commence until after the primary lesion has healed. Hanschell believes that the disease does not usually occur in the circumcised. The primary lesion is an erosion with clean edges, and is surrounded by a reddened zone, but with only slight infiltration and induration. The base of the ulcer is usually whitish-grey.

Adenitis.—The incubation period of adenitis is three to four weeks after coitus,but it may be as long as six weeks to two months. The disease generally commences with remittent pyrexia, which may precede the actual localizing signs, and may be mistaken for typhoid. Soon, subacute inflammatory swellings of the groin glands are noted. The inflammation may be unilateral or bilateral ; while the oblique glands are most frequently affected, at times the crural glands are attacked. Sometimes one groin is affected after the other. In well-marked cases, the internal iliac glands, sometimes the lumbar glands also, can be felt enlarged and tender on deep palpation. Signs of intoxication from absorption may be widespread, producing prolonged intermittent or remittent fevers, sometimes even pyrexia of 103-5° F. Rigors, vomiting, cyanosis, even slight jaundice. and considerable pain have been noted. Rheumatic-like pains in joints and painful effusions into joint cavities may also occur as a result of absorption. The affected glands slowly enlarge to the size of a hen's egg, or even larger, and after several weeks, it may be months, the swelling gradually subsides (Fig. 104). Usually, the periglandular connective tissues inflame, and the integuments become adherent until suppuration ceases. At other times fistulous tracks form, and continuously exude a clear sticky fluid. The most striking clinical feature in the male is the extensive inflammation of the periglandular tissues with comparatively little pain and suppuration. The following stages are recognized :—

Fig. 104.—Fully developed climatic bubo in right groin, showing also small primary lesion on the corona penis. (*A. H. Walters.*)

(1) A firm solitary gland, with no apparent causative lesion other than a recently-healed ulcer on the genitalia.

(2) A firm solitary gland adherent to overlying skin and deeper tissues. Adjacent glands are enlarged, including external iliac glands, palpable as a mass above Poupart's ligament. The affected glands tend to coalesce.

(3) The glands in the groin soften and fluctuate. If incised, a cavity is disclosed, trabeculated by coarse, fibrous strands.

(4) The softened gland-mass ulcerates through the skin, and spontaneous fistulation occurs. Secondary infection follows.

It was formerly believed that lymphogranulomatous adenitis was unknown in women (Hanschell, 1926), but it is now becoming recognized that typical inguinal poradenitis does occur, though inguinal bubonic manifestations are, on account of the different anatomical disposition of the lymphatic system in the female, comparatively rare; nevertheless, Galloway (1926) recorded his familiarity with typical inguinal buboes in Chinese and Japanese prostitutes in Singapore. Most of the cases of inguinal buboes in women who have given a positive intradermal test (*see* below) have been reported among prostitutes by French writers, though definite evidence of the infection of wife by husband has been obtained in an English case under the Editor's care.

Esthiomène and stricture of the rectum.—Esthiomène is an ulceration of the vulva associated with elephantiasis of the labia, formerly thought to be tuberculous. Stannus and others now believe that esthiomène is the counterpart of lymphogranuloma inguinale in the male. It has been recorded in all the countries of Europe and America, but there are very few references to it among tropical races, though Chesterman on the Congo found typical cases amongst the native women, and also saw the genito-ano-rectal syndrome there. Gray and Yieh, from Shanghai, described four cases in Chinese females. The primary lesion is probably hidden in the posterior wall of the vagina, and the ano-rectal lymphatic gland is the first to be attacked. The infiltration of this gland extends, *via* the lymph-flow, to the anterior part of the vulva, and posteriorly to the rectum, resulting in the *genito-ano-rectal syndrome*, and finally scarring of the glands leads to rectal stricture.

Fibrous stricture of the rectum, in both sexes, is probably due to the same virus. Authorities are now agreed that syphilis cannot be held responsible. Rectal stricture appears to be more frequent in Europeans than in native races, though Maxwell reported it comparatively frequently in China; Gray recorded it in both sexes in Nigeria, and Chesterman on the Congo. Rajam, in Madras, in a clinical study of lymphogranuloma and allied conditions, reviewed 183 cases of poradenitis, and found buboes in 99 males and 2 females, and the genito-anal syndrome in 18 males and 8 females. The virus spreads from the initial site of implantation by the lymphatics to the inguinal and pelvic glands, and later the lymphatics of the anus and rectum become involved, producing at first proctitis and, later still, stricture of the rectum. The following varieties are recognized:—

(1) Anal stricture in women associated with esthiomène.

(2) Annular rectal stricture.

(3) Tubular rectal stricture.

(4) Rectal communicating strictures from ulceration between the rectum, bladder, vagina, prostate and seminal vesicles.

In 1932 Frei reported that 80 per cent. of cases of the genito-ano-rectal syndrome gave a positive intradermal test.

Extra-genital infections.—Extra-genital infections have been recorded on the tongue, followed by glandular enlargements in the neck, by Curth; in the axilla by Hellerström; and on the foot by Lépinay and Grévin. A possible relationship with regional ileitis (Crohn's disease) was suggested by Likely and Lisa; they recorded a case in which multiple granulomata of the ileum were present with frank lymphogranuloma of vulva, vagina and rectum.

Ocular lymphogranuloma.—This was described by Macnie (1941). The whole globe may be covered with granulation tissue and the washings of the conjunctival sac will infect monkeys. Curth and Sanders found that a number of cases of uveitis and kerato-conjunctivitis gave positive intradermal tests; sometimes there is conjunctivitis with ciliary congestion. Fundus changes have been reported, also peripapillary œdema, dilatation and tortuosity of the veins.

Complications.—Sometimes, if too much lymphatic tissue is removed by excision of the glands, an elephantoid condition of the leg and scrotum on the affected side may develop (Fig. 105). This is a grave objection to surgical interference, added to the fact that secondary sepsis is very likely to ensue. Rupture of extensive lymphogranulomatous suppuration into the bladder has been recorded.

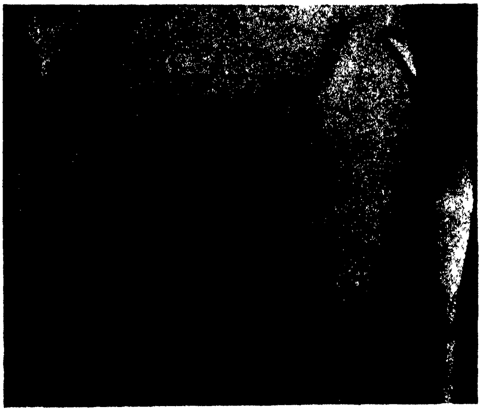


Fig. 105.—Climatic bubo two months after incision and circumcision, showing sinus formation. (*H. Wolfe Cowen.*)

Diagnosis.—The diagnosis of climatic bubo and lymphogranuloma inguinale has been placed upon a scientific basis by the introduction of the intracuti-reaction (intradermal test) of Frei (1925), which is now known as the Frei-Hoffmann reaction. The antigen was originally prepared from the inflamed gland tissue.

Frei's method of preparing antigen for the skin test consisted of withdrawing the pus from a gland which has undergone softening, but not fistulation. The aspirated pus is mixed with physiological saline, in the proportion of one part to five parts in a sterile tube, and immediately put up in ½-c.c. to 1-c.c. doses in Jena hard glass ampoules. Thus prepared, it is heated to 60° C. for two hours over a water bath, and the following day at 60° C. for one hour. The antigen should be preserved at a low temperature unexposed to light. Tests must be repeated every three months, and should give negative reactions in skin of normal and control patients suffering from *ulcus molle*. Careful experiments at the

Albert Dock Hospital, London, with a controlled antigen prepared as above, have been satisfactory.

A. H. Walters modified the preparation of the antigen for routine use as follows:

The affected gland, surgically removed, is placed in a sterile glass dish. It is then cut in half and two equal portions are placed in sterile Petri dishes marked 1 and 2. In specimen No. 1 the inner pin-point of necrotic material is macerated in physiological saline and inoculated at once into the inguinal region of guinea-pigs. Specimen No. 2 is macerated in physiological saline in a dilution of 1 in 10 by weight, and then macerated in a water bath at 60° C. for one hour; it is then filtered under strict aseptic precautions through fine Whatman paper in order to remove larger masses.

On receipt of positive animal inoculation results, three batches of antigen are pooled and subjected to further inactivation at 60° C. for one hour on each of two consecutive days. Emulsified brains of mice infected with lymphogranuloma have been employed. These extracts are more easily obtainable and can be standardized, but pseudo-positive reactions occur and may lead to confusion, while reactions may be obtained in normal persons with intradermal injection of normal brain tissue. Rake and his colleagues prepared an extract of lymphogranuloma virus on egg yolk sac. It is known as *lygranum*. When tried out by Sulkin in a series of cases the results were conclusive.

Ottolina (1941) claimed that intradermal injection of 0·3 c.c. of cerebrospinal fluid from a previously proven case of lymphogranuloma gives a positive reaction. The cerebrospinal fluid is concentrated *in vacuo* from 10 c.c. to 2 c.c. before injection.

The Frei Hoffmann test.—The test is carried out on the same lines as the Dick or Schick sensitization tests: 0·1 c.c. of antigen is administered intracutaneously in the forearm, causing a wheal 8–10 mm. in diameter. Physiological saline or *Dmelcos* chancroid antigen is administered on the other forearm as control. A positive result usually appears at the end of 24–48 hours and may vary in size from a circle of 1½ in. in diameter to a considerable reaction about 3 in. in diameter. German writers have noted a hard mass ("*Ein harter Knochen*") of infiltrated skin which may persist for a few days. This never occurs in negative cases.

The Wassén test consists of producing a fatal encephalitis in mice by inoculation of the virus.

The disease must be differentiated from soft sore, filarial adenitis, and plague, especially the ambulant form. In China especially lymphogranuloma buboes have to be distinguished from *pestis minor*; they have also to be differentiated from femoral hernia, but these two conditions may be associated. Tularæmia may also have to be differentiated.

Blood changes.—There is usually a leucocytosis accompanying the suppuration. In the Editor's cases this has invariably been so; the leucocyte counts vary from 8,000 to 27,000, but no cell-type is particularly affected.

Serological changes.—Hyperglobulinæmia is constantly present. The total proteins are between 8·1 and 10·8 per cent. in florid cases. The serum albumin is about 8·9 per cent.; serum globulin 3·9 to 5·6 per cent.

A *complement-fixation* test has been described by McKee and his colleagues. The antigen, *lygranum* (M.L.), stored at freezing point, is made from infected lungs of mice ground up to make a 10 per cent. suspension.

The readings are taken at the end of thirty minutes at 37° C. The lowest initial dilution of serum is 1 in 2.

Treatment.—In the lymphogranulomatous stage the inflamed gland, if discrete, can be excised, and the spread of further mischief appears to be avoided, but surgical interference to lay open the suppurating sinus or remove large masses of lymphatic tissue should be strongly deprecated for, as a result, the gland tissue may become secondarily infected with pyogenic organisms, a permanent lymphatic sinus may form, or chronic lymphatic obstruction may ensue. Usually, excision of the mass when suppuration is present is not followed by clean and rapid healing, but by the formation of sinuses (Fig. 105). Stammers and Law found that surgical removal of the originally infected "feeding gland" may lead to the subsidence of a larger group of secondarily involved glands.

During the acute stage of the disease, treatment should consist of rest and the application of soothing dressings.

Protein-shock therapy is often followed by dramatic results, and the Editor has had considerable experience of this method of treatment. It is especially advantageous when suppuration has commenced, and should be combined with *aseptic aspiration* of the gland. This aspiration may have to be repeated several times.

Typhoid-paratyphoid vaccine (T.A.B.), or "Pyrifer"[1] is employed, commencing with 50 million given intravenously and gradually increasing to 200 or 300 million, injections being given every third day. Two or three reactions are usually required before the buboes dry up and the surrounding induration disappears. This treatment should be combined with rest in bed, and antiphlogistine dressings. When there is active suppuration it is advisable to aspirate, making a small opening with a tenotomy knife, packing with gauze, and using silkworm stitch as a seton.

Vaccine therapy.—The vaccine is prepared by excising a convenient portion of the gland mass, which is cut up into small pieces, dehydrated over calcium chloride, emulsified in saline and injected in increasing doses every second day, but no reliable results have so far been obtained by this method.

Treatment by drugs.—*Tartar emetic.*—Intravenous injections of tartar emetic have been used since 1925. Eight to fifteen injections of from 5 to 10 c.c. of a 1 per cent. solution are required. The pentavalent compounds of antimony—such as neostibosan in recognized doses—have also been employed with apparent success.

Anthiomaline (Lithium antimony tartrate) has been given intravenously or intramuscularly. Stammers and Law commence with a dose of 0·5 c.c. (6 per cent. solution); they increase each dose by 0·5 c.c. up to 2 c.c. twice weekly to a maximum total of 20 injections. Normally only 10 are required. The average length of treatment in first and second stages is about four weeks.

Sulphonamides.—MacCallum and Findlay, by means of chemotherapeutic experiments on the virus of lymphogranuloma in the mouse, have shown that sulphonamides have a definite value. At present it is impossible to say why the virus of lymphogranuloma inguinale alone is susceptible to chemotherapeutic action, while so many other viruses are insusceptible, but the evidence so

---

[1] Pyrifer is a *Bact. coli* preparation in strengths from 50–500 million, prepared by Aristopharm Ltd., Switzerland.

far obtained seems to point to the fact that living virus may still be obtained from the brains of certain mice after prolonged treatment with sulphonamides.

In the treatment of the disease in man Montel (1937) in Indo-China found the French preparation, rubiazol, curative, if given in courses over a prolonged period. Earle (1939) reported on the value of sulphapyridine, but recent reports indicate that in actual practice the results are disappointing.

Treatment of rectal stricture.—The treatment of rectal stricture is difficult. Palliative measures consist in dilating by graduated bougies and injecting antiseptic solutions to cure the ulceration. Operative measures depend entirely upon the type of stricture present ; Lockhart-Mummery gives the following alternatives : internal proctotomy ; complete proctotomy ; excision of the stricture or of the rectum ; and colostomy. Bensaude and Lambling, on the other hand, consider diathermic dilatation to be the best method, applied for twenty minutes every two or three days, for ten to twelve applications. Oil-soluble local anæsthetics, such as proctocaine, are best for post-operative rectal pain.

The medical treatment of rectal stricture and esthiomène has been improved by the introduction of sulphonamides. Shropshear claimed success with sulphapyridine, in doses of 2 grm. daily, for fifteen days, with a seven- to ten-day interval, after which the course is repeated. Two patients required 108 grm. in two fifteen-day treatments before symptoms disappeared. In women sulphapyridine checks leucorrhœa and heals the ulcers.

CHAPTER XXXVIII

ULCERATING GRANULOMA OF THE PUDENDA

Synonym. Granuloma Venereum.

Definition.—An infective and granulomatous condition of the pudenda, widespread in some parts of the tropics, conveyed by sexual contact and auto-inoculation.

Geographical distribution.—Ulcerating granuloma is widely diffused in India, Guiana, Brazil, West Indies, Porto Rico, Papua, Pacific islands, and Northern Australia; sporadically it occurs in the Southern United States, on the West Coast of Africa, and in Southern China. De Vogel relates that in the southern region of Dutch New Guinea this disease appears in epidemic form and threatens the extinction of the local tribes. In only one case has spontaneous cure been observed.

Ætiology.—There is good reason for believing that the disease is generally, though not invariably, venereal; very rarely, extragenital lesions have been observed. Cleland and Strangman in Australia, Flu in Surinam, and Aragão in Brazil described certain parasitic bodies within the large mononuclear cells from scrapings of the lesions. The organism is like a short bacillus with rounded ends, and measures 1 μ by 0·2 μ; it was described and named *Calymmatobacterium granulomatis* by Donovan, and later by Araujo. Later, this organism was re-studied by E. L. Walker, who considered it to be a capsulated intracellular diplococcus, probably *Bacillus mucosus capsulatus*, one of the Friedländer group. The secondary invader may be the non-hæmolytic anaërobic streptococcus described by Meleney (p. 634).

Dienst and Greenblatt (1943) have not confirmed previous observations, and now think that the Donovan bodies are protozoa, in no way related to bacteria (the diphtheria group). The organism is selective for its particular host, reproduces by multiple segmentation within endothelial cells and is affected by antimony. The bodies are further distinguished by retaining basic fuchsin stain when exposed to weak decolorizing agents. The smear from an ulcer is fixed, flooded with 0·5 per cent. aqueous fuchsin for two minutes, then washed with water and 0·5 per cent. citric acid until the dye ceases to leave the smear (5 sec.). The film is then washed in water and counterstained with 1 per cent. aqueous aniline blue for 5 minutes.

Age and sex.—Ulcerating granuloma has not been recorded before puberty; it has been found only after the age of 13 or 14, and up to 40 or 50. It occurs in both sexes, but more often in women, especially where polyandry is practised.

Pathology.—Histologically this disease is allied to rhinoscleroma, and the close association between these two diseases in Sumatra has been emphasized by Snijders. On microscopical examination the new growth at the margins of the sores is found to be made up of nodules, or masses of nodules, consisting of round cells having large and, usually, badly-staining nuclei. These cell-nests of Malpighian cells are embedded in a delicate fibrous reticulum. An important feature in the histopathology is a peculiar pathognomonic cell described by Pund and Greenblatt (Fig. 106). It is a large mononuclear varying from 25 to 90 μ in diameter, probably derived from a plasma cell. The specific cell, laden with the so-called Donovan bodies, can be shown best by the *Dieterle silver impregnation* method in which these bodies appear as dark brown or black elongated ovoid masses with intense bipolar staining. The nodular masses are, for the most part, covered by epithelium, their under-surfaces merging gradually into a thick, dense, fibrous stroma in which small clusters of similar round cells are here and there embedded. The growths, though very vascular, contain no hæmorrhages; and there are no signs of suppuration or of caseation, no giant cells, and no tubercle bacilli. In vertical section of the small nodules the round-cell mass will be found to be wedge-shaped, the base of the wedge being towards the surface; the deep-lying apex is usually pierced by a hair or two. The growth is found around sebaceous follicles, blood-vessels, lymphatics, and sudoriferous glands; but it is especially abundant, and most deeply situated, around hair follicles.

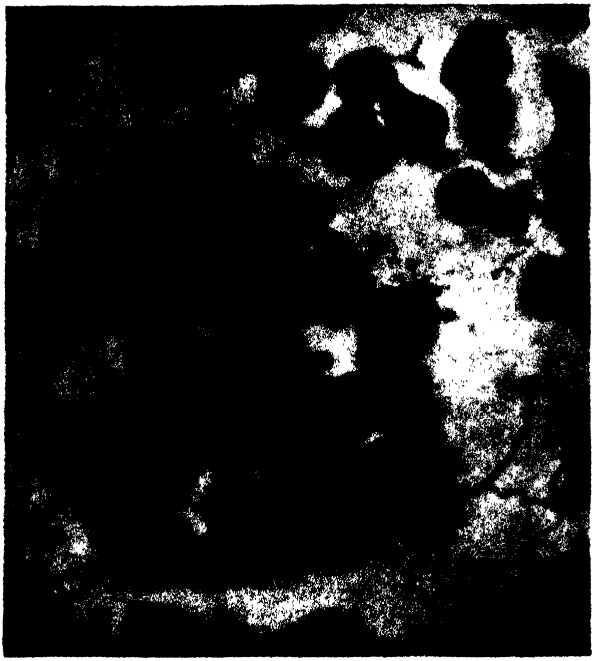


Fig. 106.—Ulcerating granuloma of pudenda showing the pathognomonic cell and contained Donovan bodies. (*After Pund and Greenblatt, "Archives of Pathology."*)

Symptoms.—The incubation period appears to be comparatively short, from two to eight days after sexual contact, but it may be as long as twelve weeks. The disease commences in the great majority of cases somewhere on the genitals, usually on the penis or labia minora, the pubes, or groin, as an insignificant, circumscribed, nodular thickening and elevation of the skin. The affected area, which on the whole is elevated above the surrounding healthy skin, and covered with a very delicate, pinkish, easily-rubbed-off epithelium, excoriates readily, exposing a surface which tends to bleed and break down, although rarely ulcerating deeply. The disease advances in two ways: by continuous excentric peripheral extension, and by auto-infection of an opposing surface. It exhibits a distinct predilection for warm and moist surfaces, particularly the folds between the scrotum and thighs, the labia, and the flexures of the thighs (Fig. 107). Its extension is very slow, years elapsing before it covers a large area. Concurrently with peripheral extension, a dense, contracting, uneven, readily breaking down scar forms on the surface travelled over by the coarsely or finely nodulated elevated new growth which constitutes the peripheral part of the diseased area. Occasionally, islands of active disease spring up in this scar tissue; but it is at the margin of the implicated patch that the special features of the affection are best observed. In cases of long standing the partially-healed areas are covered with thin depigmented skin and thus show up as white patches.

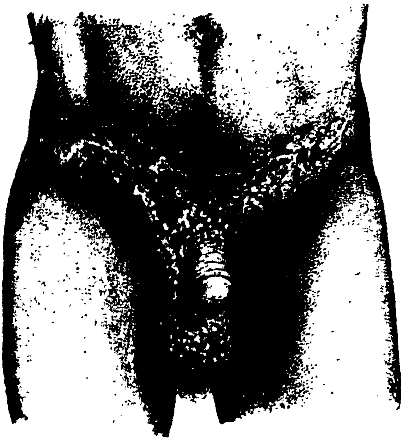


Fig. 107.—Ulcerating granuloma of pudenda in male.

In the female (Fig. 108) the disease primarily attacks the crura of the

[redacted]

Fig. 108.—Ulcerating granuloma of pudenda in female. Au
(*Dr. H. Basedow*,

clitoris, thence extending into the vagina, over the labia, and along the flexures of the thighs. The women thus affected are rendered sterile. In the male the disease may spread over the penis, involve the glans, scrotum, and upper part of the thighs (Fig. 109). Occasionally, the glans penis is not involved. In either sex it may spread in the course of years to the pubes, over the perineum, and into the rectum, the recto-vaginal septum in the female ultimately breaking down. At times, a profuse watery discharge exudes, and even drips from the surface of the new growth, soiling the clothes, soddening the skin, and emitting a peculiarly offensive odour. In this condition the disease, slowly extending, continues for years, giving rise to inconvenience, and perhaps seriously implicating the urethra, vagina, or anus, but not otherwise materially impairing the health. In neither sex do the lymphatic glands become affected. The disease continues entirely local, but in the process of cicatrization the lymph-channels may become blocked, and pseudo-elephantiasis of the genitalia may occur. Impassable strictures of the urethra may result, and recto-vaginal fistulæ are common. It may cause death by eating its way into the bladder, causing septic cystitis, as in a long-standing case under the Editor's care.

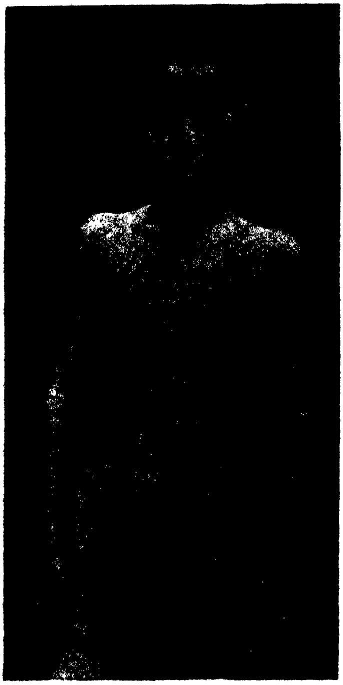


Fig. 109.—Ulcerating granuloma of face and penis in a Chinaman. (*Dr. B. Hawes.*)

Diagnosis.—Malignant and syphilitic ulcerations of the groin are common enough; the disease under notice, however, differs widely from these — clinically, histologically, and therapeutically. It is characterized by extreme chronicity—ten or more years; by absence of cachexia or of any tendency to cause death; by non-implication of the lymphatic system as a whole, and by non-amenability to mercury and iodide of potassium.

The disease which it most resembles is lupus vulgaris. From this it differs inasmuch as it is practically confined to the pudendal region; tends to follow in its extension the folds of the skin; and is not associated with the tubercle bacillus, giant cells, caseation, or other evidences of tuberculous disease. Unless complicated by a coincident syphilitic infection, the Wassermann reaction is negative. The inefficiency of anti-syphilitic treatment soon convinces the physician that the ulceration is not due to this disease. Its characteristic mode of spread suffices to distinguish it from epithelioma and carcinoma. The discharges from ulcerating granuloma have, moreover, a peculiar acrid smell. Pund and Greenblatt described a fungating form affecting the cervix uteri in negresses, which greatly resembles the ulcerative and vegetative type of carcinoma of the cervix. It has also to be distinguished from gonorrhœal endocervitis and from simple erosions.

Treatment.—Scraping and caustics, including the actual cautery, have been freely employed ; but, although some improvement may be effected, new nodules almost invariably spring up in the resulting cicatrix. Until recently, complete excision, where practicable, offered the best chance of permanent cure ; such a proceeding had to be undertaken before large areas and important passages had become involved.

Judging from its relatively superficial nature, and close resemblance to lupus, it seemed probable that ulcerating granuloma might prove amenable to some form of radiotherapy. This is actually the case, and X-rays, originally suggested by Sequeira and Macleod, have been successfully employed in some cases in Madras. Treatment by intravenous injections of tartar emetic, introduced by Aragâo and Vianna in 1913, has also proved successful ; improvement usually sets in, and, although in a small proportion of cases relapses occur, in the vast majority the cure is radical. The drug should be injected on alternate days, commencing with ½ gr. dissolved in distilled water and gradually increasing by the same amount up to the maximum individual dose of 2 gr., but the total amount required to effect a cure varies within wide limits. The Editor had one case with a limited suprapubic lesion which healed completely after a total of 17½ gr., while others required 170 gr. or more. Cicatrization usually takes place rapidly, but indolent ulceration may persist. Apparently stibacetin, neostibosan, stibenyl. and other pentavalent compounds of antimony are more efficacious than tartar emetic. From 3 to 4 grm. of the drugs is necessary. Giglioli, in British Guiana, gave two courses of seven intravenous injections with 45 days between each course. Each injection consisted of 0·1–0·6 grm. of stibenyl (stibacetin) dissolved in 20 c.c. of normal saline. He achieved cures by these means in cases resistant to tartar emetic. On the other hand Earle considered *fouadin* (a trivalent antimony salt) efficacious (*see* p. 686). Stibophen is another similar antimony preparation. The Editor has found it advisable to dress the open granulations daily with an ointment containing 1 per cent.[1] of antimony tartrate in white vaseline. It should be left on the sore for two hours, then wiped off carefully, and the sore washed with boracic solution and dressed with boracic ointment. Intermittent dressing with eusol helps to keep the surface clean. Radiant heat applied to the ulceration has proved beneficial, while touching indolent spots with a silver-nitrate stick will sometimes promote healing. When the sore is of limited extent, excision and subsequent skin-grafting may be advisable, but a wide margin of healthy skin should be removed, or recurrence will most certainly take place. Tartar-emetic treatment may be combined with X-rays and with protein-shock treatment (Hanschell). These shock treatments should alternate with tartar emetic injections. Operative measures, such as the amputation of a badly ulcerated glans penis, may become necessary.

In addition to medicinal means, it is often necessary to open up sinuses and to cauterize undermined margins by the electric cautery.

Many observers have drawn attention to types of ulcerating granuloma which are unaffected by antimony. F. L. Meleney has noted the curative action of *zinc peroxide* in the treatment of anaërobic organisms in acute surgical infections. This preparation had been used since 1903 by French and German surgeons, but for many years fell into disuse. Now it has been applied anew by Meleney in chronic ulcerations due to non-hæmolytic anaërobic streptococci which have hitherto resisted other forms of treatment. The standard preparation of zinc peroxide is one which, when sterilized and suspended in distilled water, consistently yields oxygen while itself remaining soft. It must be rubbed into the wound, especially at its spreading margins, in gangrenous infections of the skin due to synergistic bacterial action, and in undermining burrowing ulcers of the non-gangrenous type.

---

[1] To make antimony-tartrate ointment, the necessary amount of antimony tartrate is first dissolved in a small quantity of liquid paraffin and then made up to strength with white vaseline. The ointment must not be spread on the healthy skin.

Fig. 110.—Ulcerating granuloma of the pudenda infected with non-hæmolytic streptococcus. (*Dr. Butterfield.*)

To show healing with zinc peroxide treatment and extensive scar-tissue formation.

The liberation of oxygen depends upon the presence of water, and therefore zinc peroxide cannot be employed in oily solutions. The best preparation is that of the Du Pont Chemical Co., Niagara Falls. It must be sterilized at 140° C. for four minutes; 5–25 grm. are put in large test-tubes, the contents of which are mixed by means of a syringe with enough distilled water to give a homogeneous suspension with the consistency of 40 per cent. cream. It is then spread so as to come into contact with every part of the infected surface, particular care being taken to see that it gets under the undermined skin and into the sinuses, for which purpose it is frequently necessary to use a short catheter. Strips of gauze or silk are dipped into the suspension, and introduced into the sinuses. The dressings should be changed daily, but in painful cases they may be left for two days. The Editor has observed a very serious case successfully treated in this manner when all other measures had failed (Fig. 110). It was also found advantageous to syringe out the sinuses with hydrogen peroxide. All sinuses must be thoroughly opened.

Sulphonamides, especially sulphapyridine, have been successfully employed at this stage. Ross and others recorded success with 3 grm. daily for fourteen days in early lesions. Earle regarded sulphonamides as useful adjuvants to antimony treatment.

Prophylaxis.—As this disease is most certainly spread by sexual connection, prevention consists in the avoidance of illicit intercourse, especially with native women.

Section VII.—TROPICAL SKIN DISEASES

CHAPTER XXXIX

NON-SPECIFIC, BACTERIAL, AND FUNGOUS SKIN DISEASES

I. NON-SPECIFIC SKIN DISEASES

Leucoderma, or vitiligo, is extremely common throughout the tropics, and is by no means confined to any particular race. Almost any part of the body may be affected. The atrophied, unpigmented patches of skin slowly enlarge peripherally, and may coalesce. Occasionally the whole body is affected, and a certain amount of symmetry may be observed; the hair of the affected parts may also become white (Fig. 111). The texture and glands of the skin remain normal. The ætiology of the disease is unknown.

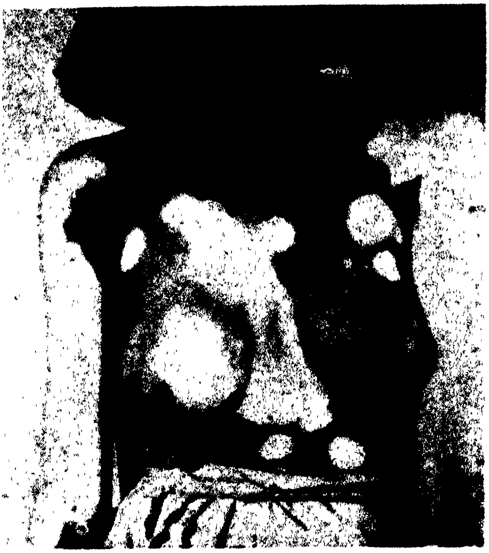


Fig. 111.—Leucoderma. (*Dr. H. K. Giffen.*)

Treatment.—*Bouchi oil* injections have for many years been employed by the Calcutta School of Tropical Medicine. The oil is extracted from the seeds of *Psoralia corylifolia.* Maplestone used it as an injection in conjunction with intestinal antiseptics. The oil is the same as that commonly used for external application. The dose is 0·05 to 0·1 c.c. intradermally at the margins of the patch; the number of injections varies according to its size. After two to three weeks the formation of pigment is noticed, and gradually spreads. A second or even a third series of injections may subsequently be given.

It is possible that cases with a positive Wassermann reaction are syphilitic and may be benefited by antisyphilitic treatment. Care must be taken not to mistake this condition for the depigmentation which is commonly seen in macular leprosy and yaws.

CHELOID

Synonym. Keloid.

The term cheloid is applied to an overgrowth of fibrous tissue in the cellular layers of the corium. Hypertrophic scars are common enough in Europeans consequent upon surgical scars or burns, but some Europeans are predisposed to develop the extensive hyperplasia known as cheloid. Central African negroes are especially liable, and in some tribes cheloidal scars on the back, thigh or chest constitute a readily recognizable tribal mark. Similar fibrosis may occur in these people after a cautery, a healed syphilitic chancre, or even mosquito-bites.

When fully developed, the growth is well defined ; on a white skin it is pinkish or brownish, but it has a distinct red or chocolate tinge on a dark person. Growth takes place very slowly and, rarely, sarcomatous changes may supervene in the fibrous tissue. The growth may cause intense pain or a continuous ache when forming.

Treatment.—The most efficacious method, according to Macleod, is by radium. A full-strength radium plate is screened off by a silver sheet 1mm. in thickness. The exposure should last 18–30 hours. Less brilliant results are obtained by CO_2 snow, especially in early lesions. Electrolysis (3 ma.) is also useful, while occasionally X-rays are satisfactory.

Keloid ought not to be diagnosed as nodular leprosy, but the mistake has been made.

II. BACTERIAL SKIN DISEASES

ULCUS TROPICUM

Synonym. Tropical Sloughing Phagedæna.

Geographical distribution.—Tropical ulcer is common in most tropical countries, particularly in those with a hot, damp climate, principally in the jungle. These sores are often named after the regions in which they are specially prevalent—Mozambique ulcer, Yemen ulcer, Naga sore (Assam), etc.

Occasionally this disease assumes epidemic proportions. Lloyd Patterson described one such epidemic which " swept like a plague up the whole of Assam," seriously interfering with the efficiency of the labour force on the tea plantations.

This form of ulcer was very common among the carriers attached to the East African Force during the 1914–1918 war, and accounted for a considerable amount of invaliding, and among natives in Africa it causes an immense amount of disability. It is the commonest cause of disability amongst labourers in Malaya, the Solomon Islands, New Guinea, and indeed in the whole of Melanesia. The average stay in hospital is 141 days in younger patients and up to 232 days in older ones, so intractable are these ulcers to treatment. In the West Indies, especially in Trinidad, the ulcers are rare in infancy, and Earle stated that they occur after the fifth year and attain their maximum incidence during the third decade. In a mixed community this incidence is highest in Indians. The majority occur during periods of low rainfall and low relative humidity.

Ætiology.—Prowazek attributed these ulcers to *Spirochæta schaudinni*. Although sloughing phagedæna is evidently a germ disease, it is not readily communicated by ordinary inoculation either to man or to the lower animals. Apparently a concurrence of certain unknown conditions is essential. Lloyd Patterson, however, succeeded in producing a characteristic sore by bandaging a swab smeared with discharge from a typical sore on to the surface of an abrasion, from which the scab had been removed.

Sloughing phagedæna is apt to attack the half-starved, malaria-stricken pioneers in jungle lands, over-driven labour gangs, and soldiers campaigning in the tropics. In such circumstances a slight wound, an abrasion, even an insect-bite, or an old chronic ulcer may serve as the starting-point for one of these terrible sores. Where yaws and sloughing phagedæna are co-endemic, the sores of the former may become infected with the virus of the latter, and serious sloughing and cicatricial contractions result. The feet and legs, being most exposed to injury, are the most frequent locations of this form of ulceration; but the arms, or any other part of the body, may also be attacked. The blood-calcium content, blood-sugar and blood-urea are said to be much diminished, probably as the result of deficient dietary (McCulloch). On the other hand, the Editor has observed several severe cases in otherwise healthy and well-fed Europeans in whom a dietetic deficiency could hardly be seriously considered.

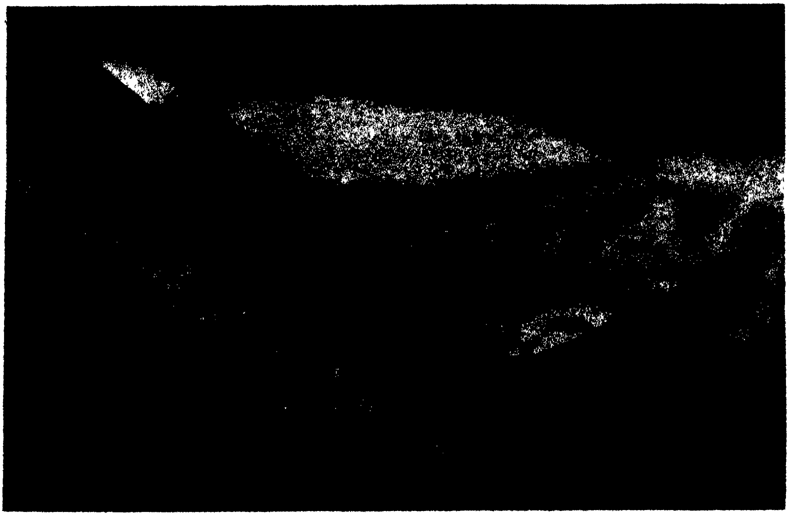


Fig. 112.—Ulcus tropicum.

Clements in Melanesia and James in the Solomon Islands were strongly of the opinion that diet deficiencies (especially B_1), debility and climatic factors combine in predisposing to ulcus tropicum. For instance, the incidence in sago-eaters is vastly greater than in those who subsist on taro. Tropical ulcer is rarer in West African native troops, whose diet includes a ration of red palm oil, than in East African troops, who do not receive this. Some consider that fusiform bacilli and spirochaetes play a considerable part in tissue-destruction. A close relationship with chronic malaria appears to be possible in the epidemic form of this disease, and stress is laid upon the importance of Buxton's line of separation between the malarial and non-malarial Pacific islands, which also marks the separation between phagedaenic and ulcer-free islands. It is apparently true that the virulence of the organisms responsible for ulcus tropicum is increased by transmission amongst susceptible people.

Symptoms.—If the disease occurs in previously sound skin, the first indication is the formation of a larger or smaller bleb with sero-sanguinolent contents. The bleb may be attended with some pain and constitutional disturbance. When, in the course of a few hours, the bulla ruptures, an ash-grey, moist slough is exposed. The sloughing process rapidly extends in all directions until the skin and subcutaneous fascia over an area of an inch to many inches in diameter are converted into a yellowish, moist, horribly stinking slough. After a few days the centre of the slough begins to liquefy, the sore still continuing to extend at the periphery. In the course of a week or longer the sloughing process may cease and the slough be gradually thrown off (Fig. 112). Then it is seen that not only have the skin and superficial fascia been destroyed, but in bad cases possibly muscles, tendons, nerves, vessels, and even the periosteum of the bones, have shared in the gangrenous process. Fortunately, in many instances, the deeper structures are spared, the disease being relatively limited and superficial. Sometimes, however, important structures, including joints, bones, and large blood-vessels, are destroyed; in such cases, even if life be spared, great deformity may ensue from different forms of ankylosis, or from strangulation of a distal part by a contracting cicatrix, necessitating amputation (Fig. 113).

Diagnosis has to be made from the ulceration of yaws, syphilis, amoebic ulceration of the skin, oriental sore, varicose ulcers, and veld sore, and is usually not very difficult, a final diagnosis being arrived at by exclusion.

Treatment.—As recent observations in Kenya Colony and Tanganyika Territory have shown that dietetics play an important part in the production of ulcus tropicum, it is of the first importance to correct any cachectic state. Thus, good food, fresh vegetables, lime-juice and quinine are almost invariably indicated. Corkhill in the Sudan found that much the same conditions hold there; cod-liver oil dressings, for instance, combined with a liberal vitamin A dietary give good results. Opium in full doses, not merely to assuage pain, but on account of its special action on the phagedaenic process, is usually of great service.

If the sore is extensive and septic, the patient should be anaesthetized, and the surface properly scraped and subsequently swabbed with pure carbolic. Directly healthy granulations appear, the ulcer should be treated on general principles. Other authorities prefer strong commercial formalin applied lightly once a day for two or three days, followed by a bismuth paste (B.I.P.) directly a scab has formed.

James stated that ulcers and their complications accounted for most of the deaths in his hospital in New Britain. In serious cases curetting or excision is often necessary, followed by skin grafting, with or without *copper sulphate treatment*. James' method is as follows :

Copper sulphate	1 oz.
Glycerin	2 oz.

Acid carbolic, 1 drm. to oz. of resulting solution.

The copper is crushed, placed with glycerin into an enamel bowl and heated. It is then stirred and allowed to cool and a drachm of carbolic is added to each ounce of solution. The ulcer is gently cleaned with wool swabs, the limb is placed horizontally, and the solution is applied on a piece of wool the size of a pea, the application being continued for two or three minutes. A dressing of acriflavine, 1 in 1,000, on gauze, is applied and is covered by a hot fomentation. The application may have to be repeated twice daily. Most ulcers are clean after applications on two consecutive mornings, and on the fourth morning scarlet-red ointment and adhesive plaster can be applied. A somewhat similar method was advocated by Acton and Panja. Todd praised specially-prepared solutions of potassium permanganate applied on cotton wool to the sloughing floor of the ulcer. The application is continued until pain is produced.

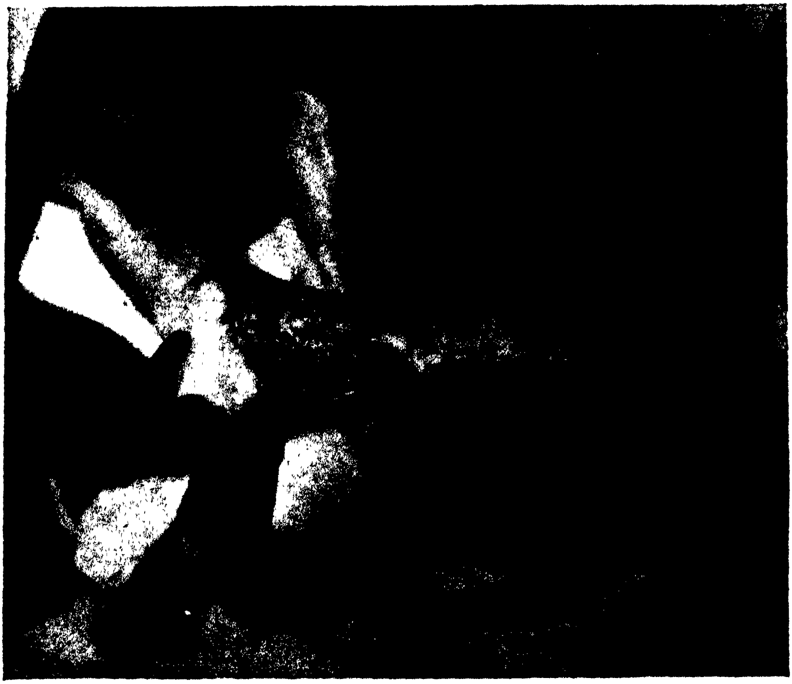


Fig. 113.—Ulcus tropicum : acute case in a European, eventually causing loss of leg.

Harley-Mason in Kenya emphasized the value of tar as an application in the mass treatment of natives, and reported on 300 cases treated in this manner. The ulcer is first swabbed out with eusol, any sloughs present are removed, and the surrounding skin is cleaned. The tar is spread on lint and changed every two or three days. Subsequently, zinc ointment is used; applications of zinc oxide and ichthyol are also recommended. Strocchi first cleansed with hydrogen peroxide and then applied gauze saturated with a preparation of arsenobenzol and iodine known as Neojodo I.C.I. Earle, in Trinidad, used applications of cod-liver and whale oil with success. Sulphonamides are of value in the early ulcers, but scarcely affect those of long standing. Sulphapyridine in daily doses of 3 grm. was found most useful. Douchet used a saturated dressing of sterile ox-bile twice daily. The bile appears to digest the sloughs.

Small superficial ulcers respond readily to powdering with iodoform, or B.I.P. dressing, and subsequent firm strapping with elastoplast after Dickson Wright's method. When elastoplast cannot be obtained, a 3-in. spiral bandage acts well. Sayers in the Solomon Islands found this method particularly suited to the natives of that region. The strapping must be left on for one week. This method is based on the principle that the best dressing for the ulcerated surface is its own discharge. Two longitudinal strips of elastoplast are applied to cover the malleoli, and further longitudinal strips are placed over the instep, over the tendo Achillis, and over the ulcer itself. A circular bandage is then applied, commencing from the toes and winding spirally up the leg. No dressing is used. After twenty-four hours, in a bad case, pus leaks through the bandage and the smell becomes objectionable. Then a plain bandage is applied, and, if the discharge is excessive, the bandage is removed after three days. At this time the ulcer may be larger, but epithelization will be occurring at the edges, and healthy granulations will appear. Spraying with insulin has been found to promote healing at this stage. The leg should then be restrapped and not touched again for a week.

There is another class of case where every simple method fails and the ulcer continues to spread in spite of the most energetic measures. In these cases total excision of the ulcer followed by Thiersch-grafting offers the only means of ultimate success. This method was used by Brennan, Anderson, Roberts in Kenya, and James in the Solomon Islands. By means of a large curved bistoury the whole of the infected tissue is removed. The ulcer is excised under spinal anæsthesia and not scraped. The resulting wound should be dressed with eusol and ointment twice daily until the surface is clean. Afterwards, a dressing of B.I.P. should be applied once daily for some days until it is certain that there is a granulating surface. The site is now treated by skin grafting. According to Enzer, when the Thiersch method fails, "pinch grafting" of small circular patches of whole skin distributed over the area should be employed. It is said that complete healing takes place in fourteen days. The grafts should be dressed with an emollient ointment, *e.g.*, *Tulle Gras Lumière* (Anglo-French Drug Co., 238, Gray's Inn Road, W.C.1). Workers in Kenya agree that the grafts usually take readily, and the stay in hospital after operation is one of twelve to nineteen days.

In contrast to the energetic measures described above, Loewenthal, in Uganda, claimed brilliant results with intravenous injections of calcium. Fifteen grains of calcium chloride in 10 c.c. of distilled water are injected intravenously daily until the cure is complete ; the dose is doubled if a case proves resistant. It is said that the offensive odour is lost in the first week, sloughs in the second, and in the third there is a healthy granulating surface with rapidly extending epithelization. However, it is probable that, though disordered calcium metabolism may play some part in the production of these ulcers, yet the results of treatment would be improved by scraping and skin-grafting.

Kerby reported zinc ionization useful in healing up residual areas of ulceration. For this purpose a 1 per cent. solution of zinc sulphate has been used at the rate of 2 ma. to the square inch for 20-30 minutes.

Veld Sore

Synonyms. Septic Sore ; Desert Sore ; Barcoo Rot.

Geographical distribution.—This peculiar ulceration is widely distributed in the tropics and subtropics wherever desert conditions exist. It has long been known in Queensland and the Northern Territory of Australia. It affected the British troops in the Sudan and South African campaigns, and caused a very considerable amount of disability in Gallipoli, Egypt, Palestine and Iraq during the 1914 18 war. It has also been prevalent in British troops in Palestine, Libya, Abyssinia, Eritrea and the Middle East during the present war. In South Africa it is familiar to sportsmen and travellers.

Ætiology.—The cause of this condition has long been obscure.[1] In 1916 Craig, in the Sinai Desert, demonstrated the diphtheria bacillus in the lesions. Whether this covers the ætiology of all veld sores cannot at present be affirmed, but that a certain proportion are diphtherial in origin may be taken as established. By sterilizing the surface of the sore with absolute alcohol and scraping the clear surface, a culture of the Klebs-Löffler bacillus was obtained on Löffler's serum. This organism was pathogenic to guinea-pigs and quails, and its lethal effects could be neutralized by injection of antidiphtheritic serum. In the serous contents of the blebs the typical granular bacillus was observed in stained preparations. (Fig. 114.)

Fig. 114.—Culture of Klebs-Löffler bacillus obtained from the veld sore shown in Fig. 115.
(Dr. H. K. Giffen, Assiut, Egypt.)

The desert sores, as the Editor observed them among British troops, occurred most frequently in men of mounted units, especially those associated with horses and camels, and more recently similar lesions have been found in cavalrymen. The rate of incidence coincides with that of a widespread epidemic of faucial diphtheria. Cameron and Muir (1942) described the lesions as they occurred in mounted units in Palestine in the present war. Acute and chronic stages are recognized. Paralyses occurred in a number of patients in whom there was no other focus of infection than the skin. Not all sores on exposed parts are necessarily diphtherial in origin; some are primary staphylococcal. In Eritrea and Abyssinia it was noted by Louw that the men of mechanical units with oil or grease on their clothing suffered less than others from septic ulceration. Excessive dryness of the skin is a predisposing factor.

---

[1] H. H. Scott (personal communication) isolated the diphtheria bacillus from a veld sore the S. African war in 1901, and succeeded in curing it by application of antidiphtheritic serum.

Symptoms.—The sores occur almost invariably on the exposed parts, mainly those covered by hairs, such as the dorsum of the hand, the fore-arm, the elbows and knee-joints. Sometimes the lesions occur on the face, over the eyebrows and on the cheeks. They may arise *de novo*, or be superimposed on some abrasion.

A regular sequence of events precedes the actual ulceration. At first a *vesicle* full of straw-coloured fluid makes its appearance, generally in the vicinity of a hair follicle; it may vary considerably in size. The pain it occasions is quite out of proportion to the size of the lesion. On bursting it leaves behind a shallow *ulcer* covered with a thin grey pellicle. The raw ulcerated surface is exquisitely tender, and it may continue to spread peripherally. (Fig. 115.)

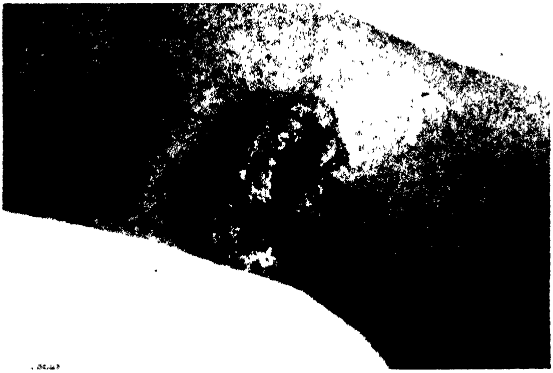


Fig. 115.—Veld sore on leg containing growth of Klebs-Löffler bacillus.
(*Dr. H. K. Giffen.*)

After the inflammatory changes have lasted two or three weeks the ulcers enter upon a *chronic stage*. At this stage they are characteristic in appearance and perhaps are more familiar to practitioners than the incipient stages. The ulcers are punched-out, circular, with undermined edges and thickened margins; their base is covered with grey-coloured and scaly débris, beneath which can frequently be distinguished an adherent membrane, but little or no pus is discharged. The peculiar ulceration which results is most intractable, and resists all external forms of medication; the edges become indurated, and the thickened tissue has a cyanotic appearance. In sores in which healing does take place, a thin paper-like scar remains for several years. The actual ulceration may continue for two years or longer.

The Klebs-Löffler bacillus can be isolated from the primary lesions; from the chronic ulcerations it is recovered with difficulty, being overgrown with staphylococci and other organisms of suppuration. The best medium is Marshall tellurite.

Diphtheritic pareses, or paralyses, have been observed in association with these sores; in one series this complication occurred in 27 per cent. Paralysis of the palate, arms and legs, and accommodation paralysis of the iris have been observed. There may be ataxia, loss of knee-jerks, anæsthesia and inordination, recalling at first sight locomotor ataxia or beriberi. Walshe pointed out that the initial local paresis is in anatomical relation to the site of the infective focus, and may be taken to indicate direct passage of toxins from the diphtheritic lesion along the neural channels to the central nervous system. Accommodation pareses, on the other hand, usually appear in the second week, no matter what the site of the local lesion may have been. Polyneuritis is usually delayed for three weeks or longer.

Treatment.—The specific treatment for this kind of ulceration is anti-diphtheritic serum, which has a very striking effect in healing up ulcers that have persisted for a year or even longer. At least 20,000 units should be given, and should be injected subcutaneously or intramuscularly in the vicinity of the sores. In the present war, sulphonamides by the mouth have been found useless, but in chronic cases staphylococcal vaccines are advocated, together with compresses of hypertonic saline, cod-liver oil dressings, and elastoplast bandages. In some cases silver nitrate stick is beneficial.

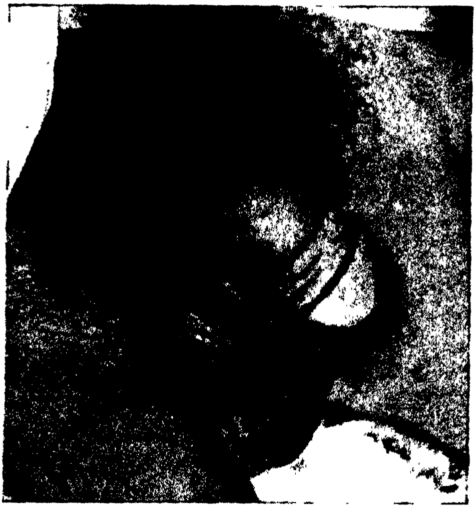


Fig. 116.—Veld sore. Primary lesion on adductor aspect of thigh ; secondary contact sore on scrotum.
(*Capt. Manton, A.D.C.*)

In staphylococcal sores sulphonamide paste and acriflavine ointment have been employed (acriflavine, 0·1 per cent.; adeps lanæ anhydrous 45 per cent.; water 100 per cent., to which is added 10 per cent. *sodii sulph.* for osmotic effect).

Prophylaxis.—Protection of exposed parts of the body, especially the knees, against abrasion in desert regions where these sores occur, is obviously indicated. Mounted men should wear knee-breeches and should not be permitted to ride in shorts. The application of antiseptic lotions to any abraded surface at the earliest possible moment is also indicated. As there is some evidence that dried horse-manure may act as a nidus of the bacillus, care should be taken to avoid contact with this as far as possible.

BOILS

The anatomical and clinical features of this painful affection are too familiar to require detailed description. Suffice it to say that a boil is produced by the proliferation of *Staphylococcus pyogenes aureus* and *albus*, *Streptococcus pyogenes*, or other pyogenic micro-organisms in the skin and subcutaneous tissue; that the organisms give rise to local and limited infiltration of the tissues with lymph, leading to necrosis, the central core being surrounded by an areola of acute inflammation; that this core is separated by a process of sloughing and so got rid of, the resulting ulcer speedily healing, and leaving a depressed scar which, when occurring about the legs, may become pigmented. Though a self-limiting disease locally, it is nevertheless capable of being inoculated elsewhere in the same individual, both through a breach of surface and also by simple contact of the discharges with the skin, the micro-organism apparently entering by a hair follicle. This auto-inoculability of boils is apt to be overlooked.

Conditions of debility, presumably by lowering resistance, predispose to boils; the subjects of diabetes are especially liable to them, the saccharine state of the blood or secretions seeming to be particularly favourable to growth of the specific germ. In the tropics, boils are the frequent accompaniment of and sequel to malaria.

Treatment.—Boils ought never, unless in very exceptional circumstances, to be poulticed. Poulticing, although it may relieve the pain of the existing boil, is apt to be followed by more boils in the area made sodden by the heat and moisture. Nor should boils be incised or squeezed. The only exception to the rule of not cutting is a boil in the scalp or axilla. In the former situation, unless opened early, they are apt, especially in young children, to burrow and cause troublesome abscesses; in the latter situation boils tend to be very indolent and painful, and do not readily break through the lax integuments.

In any situation in which the boil is likely to be irritated by pressure or clothing, it is sometimes a good plan to cover the part with a circle of wash-leather spread with soap plaster and having a small hole cut in its centre corresponding to the apex of the boil or, under modern conditions, with a specially-prepared elastoplast strip. When a boil opens, the discharge must be kept from soiling the adjoining skin, and the patient must be warned against touching the skin elsewhere with pus-soiled fingers. The parts must be frequently cleansed with 1 in 1,000 corrosive sublimate lotion, powdered with boric acid, and covered with a dry, absorbent antiseptic dressing. A threatening boil may often be aborted by touching the little initial itching or vesiculated papule with some penetrating antiseptic, such as iodine tincture, or by painting it with collodion. A very successful method is to drill slowly into the centre of the papule with a pointed pencil of hard wood dipped in pure carbolic acid. The point of the pencil should penetrate at least an eighth of an inch, and should be frequently recharged with the acid during the drilling process; the pain is trifling. In this way, in a severe attack of furunculosis, boil after boil may be aborted and the attack brought to an end. In obstinate chronic furunculosis excellent results have occasionally attended treatment by injections of an autogenous vaccine commencing with a dose of fifty millions and working up to three hundred millions of organisms.

The effect of various sulphonamides and penicillin on pyogenic suppuration is now being noted.

In sulphathiazole, given in full doses of 3 grm. per diem, we possess a specific for some cases of staphylococcal suppuration.

PEMPHIGUS CONTAGIOSUS (PYOSIS MANSONI)

Geographical distribution.—Pemphigus contagiosus is very common in

South China during the hot weather; in some years it may even be described as epidemic. It is perennial in the Straits Settlements, and it is known in Ceylon, Madras, in North Queensland, Japan, and America. European are more liable to it than native children; European adults are by no means exempt, but the native adult is rarely affected.

Ætiology and pathology.—Like impetigo contagiosa, this is undoubtedly a germ disease, caused by streptococci and staphylococci. Manson originally found a diplococcus in epidermis and in the fluid of the blister.

Symptoms.—Pemphigus contagiosus closely resembles certain forms of the impetigo contagiosa of temperate countries, and is probably a variety. The individual lesions, as can readily be ascertained by inoculation experiments, begin as minute erythematous specks, which rapidly proceed to the formation of vesicles, bullæ, or even large pemphigus-like blisters.

Pemphigus contagiosus may occur in almost any part of the body. In young children it is usually diffuse; in adults it is mostly confined to the axillæ and crutch.

Diagnosis.—Absence of constitutional symptoms, or of a history of such, distinguishes pemphigus contagiosus from chickenpox. Absence of trichophyton elements, and of a well-defined, slightly raised, festooned and itching margin, together with the presence of large blebs and scaling of the epidermis, distinguishes it from ordinary forms of body ringworm—a disease with which, when occurring in the armpits and crutch in adults, it is frequently confounded.

Treatment.—Cleanliness, the frequent use of a corrosive sublimate lotion (1 in 1,000) and a dusting-powder of equal parts of boric acid, starch, and zinc oxide, or ammoniated mercury ointment are specially effective. Sulphonamide compounds, especially sulphapyridine in full doses of 3 grm. daily to an adult, were found effective by Earle. In the school and nursery those responsible for the care of children must be informed of the contagiousness of this unpleasant affection, and measures must be instituted accordingly.

CRAW-CRAW AND ULCERATIVE DERMATITIS

Synonym. Nodular Dermatitis.

Symptoms.—The term craw-craw is very loosely applied. Emily described under this name a papulo-pustular skin affection which is common in certain parts of tropical Africa and is often the cause of much suffering to the traveller. It, or a similar disease, is by no means confined to Africa, for it is seen in patients from Ceylon and India, and Manson was at one time very familiar with it in South China. The disease begins as an itching papule, very possibly at the seat of a mosquito-bite. The itching provokes scratching, whereby some form of pyogenic micro-organism is inoculated. Pustulation follows, and is spread over feet and legs by soiled shoes and stockings, and by auto-inoculation. In this way an ulcerating, pustulating dermatitis is kept up.

In the exudate of these papules O'Neil originally found small filaria embryos which resembled the embryo of *Acanthocheilonema perstans*. Brumpt did not believe that these are examples of the embryos of *Onchocerca volvulus*, as was affirmed, but possibly they are the same as the microfilariæ described by Macfie (*see* p. 938).

Diagnosis.—The hard, horny papules of craw-craw have to be differentiated from scabies, which is common in African natives. They have also to be distinguished from the lichenoid eruptions caused by microfilaria volvulus (p. 741).

Treatment.—Emily described a very efficient treatment. Pustules are opened, crusts removed, and ulcers scraped. Boric-acid powder is then dusted freely on the parts after a thorough scrubbing with sublimate lotion (1 in 1000); borated vaseline is applied on lint, and this is covered by absorbent cotton and a bandage. The dressings are not disturbed for a week, when the parts will be found soundly healed. Similar auto-infective diseases, so common in the tropics, may be treated by prolonged soaking in a warm carbolic-acid lotion (1 in 20), followed by dry dressing with boric powder. Infected slippers, shoes, and stockings should be destroyed.

III.—PARASITIC DERMATITIS

CERCARIAL DERMATITIS (SCHISTOSOME DERMATITIS)

Cort in Michigan (U.S.A.) in 1928 drew attention to a special kind of dermatitis produced by *Cercaria elvæ*, and *C. douthitti* was soon afterwards found to cause similar lesions. In England and Wales dermatitis after bathing in ponds and reservoirs has been noted by Matheson, Taylor and Baylis as due to *C. ocellata*, a form closely allied to *C. elvæ*. The cercariæ burrow in the skin, where their heads become arrested and cause a pustular eruption. All these cercariæ are derived from different species of snails, especially *Lymnæa ocellata*. *C. elvæ* and *C. ocellata* are large cercariæ nearly 1 mm. in length overall, twice that of the bilharzia cercariæ; the tail is bifurcated and all possess two suckers. Cercarial dermatitis is commonly known as "sedge-pool itch" or "swimmer's itch," and takes the form of an itching maculo-urticarial dermatitis, later becoming papular or pustular; it may be, after a few days, actually exanthematous. It is always connected with paddling or swimming in infected waters a few days previously. A somewhat similar dermatitis is noted in association with cercarial penetration in *Bilharzia hæmatobia* and *B. mansoni* infections.

IV.—ALLERGIC AND TOXIC DERMATITIS

PYRETHRUM DERMATITIS

Pyrethrum dermatitis has been noted in Kenya, and is caused by the leaves and flowers of *Chrysanthemum cinerariafolium*, which grows at altitudes of 500–7000 feet and flowers throughout the year. The pyrethrum content is 1-2 per cent. Absorption is facilitated by constant sweating, and exposure to sunlight greatly exacerbates the lesions. Some persons on contact exhibit merely a local dermatitis; others show a widespread allergy. Itching commences at the corners of the eyes, and is followed by lachrymation, an irritating vesicular rash, peeling of the skin, and formation of painful fissures.

POISON IVY DERMATITIS (DERMATITIS VENENATA)

Many tropical plants cause dermatitis which may assume an erythematous, vesicular or urticarial form. Intimate contact with the plants or its leaves is necessary. Poison ivy (*Rhus toxicodendron*), poison sumac (*R. vernix*), poison wood (*Metopium toxiferum*) in North Eastern and Southern United States cause intense dermatitis. Repeated attacks do not produce immunity. The venom is *toxicodendrol*. Treatment consists of washing the skin with soap and water; alcoholic or oily solutions must be avoided. Clothes must be decontaminated by immersion in 1 per cent. calcium hypochlorite for twenty minutes.

OTHER FORMS OF DERMATITIS

Several other plants and flowers may cause severe allergic dermatitis, such as cypripedium (lady's slippers), *Euphorbia*, primroses, lilies and vanilla beans; sometimes also mangoes and, in Japan, lacquer made from *Rhus vernicifera*.

Iroko dermatitis.—Idiosyncrasy to wood dust is not uncommon. Iroko is a trade name for *Chlorophora excelsa*, a tree of East and West tropical Africa, and known as African teak. The dust produces the usual signs of allergy, with skin irritation, œdema of face, blepharospasm, acute coryza and pharyngitis. Other woods, such as satin wood, teak and mahogany, also produce allergy in susceptible persons.

V.—CLIMATIC SKIN DISEASES

PRICKLY HEAT

Synonym. Climatic hyperidrosis.

Prickly heat, or, as it is sometimes called, lichen tropicus, is probably a form of miliaria (not of lichen) connected with the excessive sweating incident to the heat of tropical climates in association with high humidity. It therefore occurs especially in the Red Sea, Persian Gulf, the plains of India, in Eritrea and Somaliland; in the New World, in Panama and in northern parts of South America.

Ætiology.—According to Pollitzer, the mechanism of its production depends on the non-cornification of the cells of the stratum corneum, the individual cells of which, in consequence of being sodden by constant perspiration, swell, and so obstruct the orifices of the sweat-glands, thereby leading to accumulation of sweat in the ducts. The blebs and bullæ are due to breakdown of function in the second form of sweat glands of the skin, especially the large coil sweat glands localized to the axillæ and genital regions. The miliary rash, commonly known as prickly heat, is due to dysfunction of small sweat glands, and a pemphigoid condition due to dysfunction of the large sweat glands.

In scales obtained from the lesions, E. C. Smith demonstrated yeast-like budding forms and branching mycelium of a species of Oidium, but this probably represents a secondary infection.

Symptoms.—Many Europeans in the tropics suffer from prickly heat, particularly during the earlier years of residence. Some never seem to become acclimatized, but continue year after year to exhibit their crop of prickly-heat lesions when the hot season comes round.

Though sufficiently annoying in the robust and healthy, prickly heat is not a grave affair. It is otherwise in the invalid, delicate sickly children, hysterical and, especially, parturient women; to these it may prove, by interfering with sleep and provoking restlessness, a very serious matter.

Prickly heat consists of a miliary-like eruption, generally most profuse on those parts of the body, as around the waist, which are closely covered with clothing; but it also occurs on the backs of the hands, on the arms, legs, forehead, occasionally on the face, the scalp, in fact on any part of the surface of the body except the palms and soles. The minute, shining, glass-like vesicles, and the numerous, closely-set, slightly inflamed papules, give the skin a feeling of being thickly sprinkled with grains of sand. The eruption may continue for months on end, becoming better or worse according to circumstances. The pricking and itching are often exceedingly distressing. Anything leading to perspiration immediately provokes an outburst of this almost intolerable itching—nothing more certainly than a cup of hot tea or a plate of hot soup. Long drinks, exposure to the hot sun, close rooms, warm clothing, all aggravate the distress. As soon as the weather becomes cool the eruption and the irritation quickly subside.

Blomfield (1943) divided the forms of prickly heat clinically into (1) miliaria, (2) multiple boils, (3) impetiginous, (4) pemphigous, (5) pustular with fungous infection. A special and distinct form of boil develops, consisting of insidious, painful blisters, especially on the fingers. These are deep-seated whitish swellings, very often with paronychia. An impetiginous rash is a frequent concomitant infection.

A very severe form consists of very painful symmetrical crops of blebs and bullæ in armpits and crutch. The bullæ are filled with thin pus, and are surrounded by a bright red ring of acute inflammation.

The pemphigoid state is a late stage of the disease, and is often complicated by secondary fungous infection.

Treatment.—Manifestly, the most important thing is the avoidance of all causes of perspiration—particularly the copious consumption of fluids, especially hot fluids—moderation in exercise, avoiding sea-bathing, close rooms, warm clothing, and so forth. A towel should be carried to mop up sweat. The sleeping-mattress and pillow should be covered with a finely woven grass mat, and the bed provided with what is known in the East as a " Dutch wife "—that is, a hollow cylinder, 4 ft. by 8 or 10 in., of open rattan work, over which the arms and legs can be thrown, and unnecessary apposition of sweating surfaces so avoided. A punkah at night is a great comfort. Afridol soap, containing oxymercuriotoluylate of sodium, in which mercury is in non-ionizable form, can be recommended as a preventive and a curative measure. The soap is powerfully germicidal and should be used twice daily with warm water. A firm lather should be produced in warm water and applied to the affected parts. The lather should be left to dry on the skin for a quarter of an hour so that it can exercise its full effect, after which time it can be thoroughly washed off. When this is unprocurable, hydrarg. perchlor., 1 in 1000 solution, may be used, followed by boric acid, calamine and zinc oxide in equal parts as a dusting powder. Midgley's " Medisoaps " are also recommended, especially one containing 20 per cent. carbolic acid, and a second containing mercury biniodide. Every bathroom in the tropics should be provided with some mildly astringent and antiseptic dusting powder. A very good one consists of equal parts of boric acid, oxide of zinc, and starch. This should be freely applied, after careful drying of the skin, particularly to the axillæ, the crutch, under the mammæ in women, and between the folds of skin in fat children and adults. A simple precaution of this sort saves much suffering both from prickly heat and from epiphytic skin disease. Ruge recommends rice powder containing a little *desitin*.

The frequent application of a salicylic-acid (1 dr.) and spirit (8 oz.) lotion has been advised. Pearse strongly recommends the inunction of a mixture of almond oil and lanolin in the proportion of 8 to 1. Some consider thin flannel a better wear than cotton or linen as a preventive of prickly heat. Sometimes the following powder, gently rubbed in for five or ten minutes with a damp sponge, will cure bad patches: sublimed sulphur, 80 parts; magnesia, 15 parts; oxide of zinc, 5 parts. Calamine lotion, with or without hydrocyanic or carbolic acids (2 per cent.), relieves the itching and is strongly recommended.

TROPICAL CHEIROPOMPHOLYX

This name is given to vesicular eruptions on the hands, fingers or feet.

In the majority of cases these are due simply to eczema ; others are signs of dermatitis due to external irritants, or are toxic eruptions due to ringworm infection of the toes. Owing to the thickness of the horny layer on the hand, the vesicles cannot rupture as they would elsewhere, and remain in the skin for days like grains of boiled sago. The best treatment is calamine and lead lotion with liquor picis carbonis, and sometimes the addition of weekly doses of a quarter of a pastille of X-rays, not more than four in all.

It is claimed by Fitz-Patrick that a distinct form, endemic in tropical Africa and India, is caused by an anaërobic bacterium which attacks the palmar and interdigital aspects of the hands and the plantar aspects of the feet. The following ointment is said to be specific :

Coal tar	3 parts
Powdered charcoal .	1 part
Zinc oxide . .	4 parts
Lanolin and vaseline	12 parts

The ointment is rubbed well into the affected parts, and cotton gloves or socks are worn. In conjunction with this, resorcin soap must be used.

VI. FUNGOUS SKIN DISEASES

Dhobie's Itch (Tinea Cruris) and Pityriasis Versicolor

Ætiology and nomenclature.—By the lay public all epiphytic skin diseases in the tropics—more especially all forms of intertrigo— are spoken of as *dhobie's* (washerman's) *itch*, in the belief, probably not very well founded, that they are contracted from clothes which have been contaminated at the washerman's. There are many sources of ringworm infection in warm climates besides the much-maligned dhobie.

In the tropics, native children often exhibit dry, scurfy patches of ringworm on the scalp ; and the skin of the trunk and limbs of adults is not infrequently affected with red, slightly raised, itching rings, or segments of rings, of trichophyton infection. In some cases these rings enclose areas that are many inches in diameter.

Pityriasis versicolor (*Tinea versicolor*) is also very common in the tropics. It is the usual cause of the pale, fawn-coloured, slightly scurfy patches so frequently a feature of the dark-skinned bodies of natives. On the dark-pigmented skins of negroes, Indians and dark-complexioned Chinese, the patch of pityriasis—unlike that in Europeans and light-skinned Chinese—is usually paler than the healthy integument surrounding it. The pigment in the fungus and the profuse growth of the latter conceal, as a coat of paint might, the dark underlying natural pigment of the skin, which, moreover, in certain cases seems to be affected (either increased or decreased) by the action of the fungus. The *disease is most commonly seen in young* adults, *is favoured by excessive perspiration*, and *especially by flannel* underwear, and is rarely seen in the aged.

Several varieties of fungi may be involved in the production of pityriasis; besides *Malassezia furfur*, the best-known is *M. mansoni*, of which a culture in maltose-agar produces black hemispherical colonies, black patches on the affected skin. The mycelium and spores are refractile with slow budding. The *hyphæ* are 2–3 μ, the spores 3–8 μ.

The expression dhobie's itch, although applied to any itching, ringworm-like affection of any part of the skin, most commonly refers to some form of epiphytic disease of the crutch or axilla. This infection has now become widespread in Great Britain and is endemic in many English public schools, where it is spread by infected clothes and water-closet seats. There are at least two species of parasite which in the tropics are apt to attack those situations, namely a trichophyton—*Epidermophyton inguinale*—and *Actinomyces minutissimum* of erythrasma.

E. inguinale is peculiar to man only; it is not easily cultivated, and grows slowly. On Sabouraud's agar medium it takes a week to develop, and appears first as powdery growth. The mycelium is 1 μ in diameter, often fragmented into bacillary arthrospores.

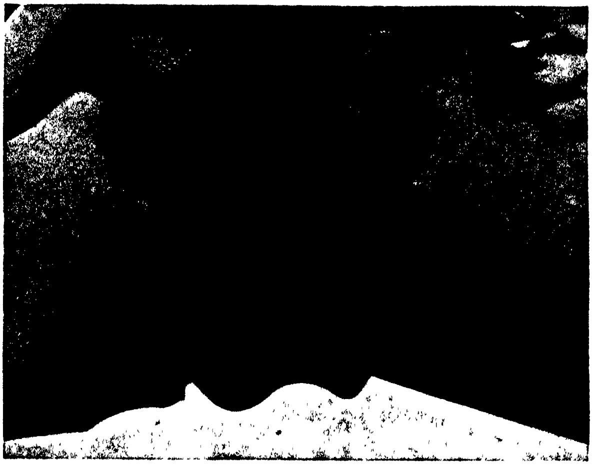


Fig. 117.—Dhobie's itch, symmetrical lesions in groins.

Symptoms.—The suffering to which certain forms of dhobie's itch give rise is often severe. In hot damp weather, especially, the germs proliferate actively, producing, it may be, smart dermatitis. The affection begins usually as slightly raised, rounded and elevated papules which spread peripherally, producing a raised festooned border covered with thick scales. The excessive irritation thus set up leads to scratching and, very likely, from secondary bacterial invasion, to boils or small abscesses. The crutch, or axillæ, or both, are sometimes rendered so raw and tender that the patient may be unable to walk or even to dress. (Fig. 117). It commonly extends backwards on the perineum and into the natal cleft about the anus. It often affects the skin under pendulous breasts and occasionally forms patches resembling tinea circinata on the thighs. The irritations thus produced are usually worse at night, and may keep the patient awake for hours. Even without treatment, when the cold season comes round, the dermatitis and irritation subside spontaneously. The affected parts then become dry, pigmented, and scurfy, and the fungus remains quiescent until the return of the next hot weather.

Diagnosis.—The diagnosis of mycotic dermatitis is usually easily made. the festooned margin is almost conclusive. If doubte xists, the microscope may be necessary; but, owing to the inflamed condition of the parts, there may be much difficulty in finding fungous elements, even when the case is certainly epiphytic. A negative result is, therefore, not always conclusive against ringworm. The mycelial elements can be distinguished in epidermal scales soaked in liquor potassæ. It has to be distinguished from *seborrhœic dermatitis, intertrigo* and *flexural psoriasis.*

Treatment.—The patient should get two pairs of running shorts, which should be worn on alternate days, the pair not in use being boiled. After a thorough use of soap and water, the application of *Vleminckx's solution* of sulphide of calcium (1 oz. quicklime, 2 oz. precipitated sulphur, 15 oz. water, boiled together in an earthenware vessel till reduced to 10 oz.; the clear sherry-coloured fluid being decanted after subsidence) every night for three or four nights generally brings about a rapid cure. If the parts are inflamed and tender, the solution should be diluted to half- or quarter-strength for the first two applications. A preliminary soothing treatment by lead lotion, or an ichthyol or hazeline cream, is desirable in such cases. A tincture of the leaves of *Cassia alata* painted on, or vigorous rubbing with the crushed leaves themselves, is equally successful. If these fail, chrysophanic acid ointment, 20 gr. to the ounce of vaseline, rubbed in twice a day until a slight erythema shows at the edge of the diseased patch, is almost invariably successful. When prescribing chrysophanic acid the physician must be careful to inform the patient of its staining effect on clothes; to warn him to stop its use as soon as the erythematous ring shows, and to be careful not to apply the ointment to the face.

More conveniently, chrysophanic acid may be prescribed in the following form with gutta-percha, and should be painted on with a brush on alternate nights.

Acid. chrysophan.	gr.xx	(1·296 grm.)
Chlorof.	ʒi	(3·5 c.c.)
Liq. gutta-perchæ	℥i	(28·42 c.c.)

Cignolin is a synthetic chrysarobin and is useful in all fungoid skin affections, in fungus of the nails, cheiropompholyx, and in psoriasis. Cignolin is apparently free from toxic action on the kidneys, and in neat concentrations it can be applied to the scalp without any danger of conjunctivitis. The prescription is cadojel (a proprietary tar preparation), 1 grm.; cignolin, 0·1–0·2 grm.; benzol, 10 grm. If cadojel is not obtainable, a suitable formula is:

Ol. cadin (deod.)	**♏xl**	**(2·368 c.c.)**
Cignolin	**gr.iv**	**(0·259 grm.)**
Benzol. rect.	**℥i**	**(28·42 c.c.)**

The combination of cignolin and tar follows the indications closely, for the former has a parasiticidal action and the latter is unrivalled for its soothing properties.

The method of application is very simple, the affected areas being painted with the solution twice daily and then covered with strips of gauze. If there is too much irritation, then the painted areas are further protected with a thin layer of Lassar's paste or calamine lotion.

The following are the other prescriptions of Cignolin which may be used for this or any other fungus affection.

1.	Cignolin	gr.x	(0·648 grm.)
	Chlorof. meth. ad	℥i	(28·42 c.c.)
	Ft. sol. = Cignolin paint.		
2.	Cignolin	gr.iv	(0·259 grm.)
	Zinc oxid.	ʒss	(1·944 grm.)
	Ol. oliv. ad	℥ss	(14·21 c.c.)
	Ft. unguentum.		
3.	Cignolin	gr.ss	(0·032 grm.)
	Liq. carb. deterg.	ʒss	(1·176 c.c.)
	Acid. salicyl..	gr.iii	(0·194 grm.)
	Paraff. moll. ad	℥ss	(15·55 grm.)
	Ft. unguentum.		
4.	Cignolin	gr.v	(0·324 grm.)
	Ichthyol	ʒss	(1·944 grm.)
	Paraff. moll. ad	℥i	(31·1 grm.)
	Ft. unguentum		

Hallow (1936) endorsed the value of cignolin treatment in his account of 310 cases treated in this manner. The patient should be isolated and kept in clean pyjamas during treatment. For three days cignolin, 2 per cent. in soft paraffin, is applied with bandages : even if one thigh only is affected, both should be treated. At the end of this period, only disinfected or non-infected clothing should be worn, and, as an additional precaution, unguentum acid. benz. should be applied nightly to the treated areas.

Tincture of merthiolate (Eli Lilly & Co.) is also effective (p. 655).

For the ringworms of the thick-skinned natives, linimentum iodi of double strength, freely applied, is the best, speediest and most efficient remedy, but it is too irritating and painful for the European skin.

Prophylaxis.—The various forms of crutch dhobie's itch may be avoided by wearing next the skin short cotton bathing-drawers and changing them daily, at the same time powdering, after the daily bath, the axillæ and crutch with equal parts of boric acid, oxide of zinc, and starch.

Ringworm of the Feet (Hongkong Foot ; Athlete's Foot ; Brocq's Eczema ; Tinea Pedis)

A peculiarly intractable infection of the soles of the feet, occurring especially amongst Europeans, is commonly observed in China and is known locally as "Hongkong foot." This mycotic infection, as identified by Dodd, is believed to be a variety of *Epidermophyton inguinale*, or, according to Beintemar, *E. interdigitale*. It occurs especially during the summer months and appears as deep-seated vesicles about the inner margin of the hollow of the sole, or on, or between, the toes at their proximal extremities ; or as a macerated condition of the skin of the interdigital clefts and of the contiguous surface ; scaling of the skin with persistent and intolerable itching is a marked feature, and it often becomes secondarily infected (Fig. 118). Often a mycotic infection of the nails and the palms of the hands is associated with it. resembling Hebra's *eczema marginatum*, which is said to be due to a special fungus, *E. floccosum*. A similar condition has been described in Turkish baths in England by Whitfield, and in swimming baths in the Southern United States, as well as among bathers in Holland. As a preventive measure the application of the following lotion is recommended :

Liq. formaldehyd. (40 per cent.)	ʒi	(3·5 c.c.)
Acid. salicyl.	ʒi	(3·5 c.c.)
Alcohol and water, equal parts .	℥viii	(227·36 c.c.)

Care must be taken to distinguish the eczema reactions which are superimposed upon foot ringworm. Where such reaction is present treatment must be directed on other lines.

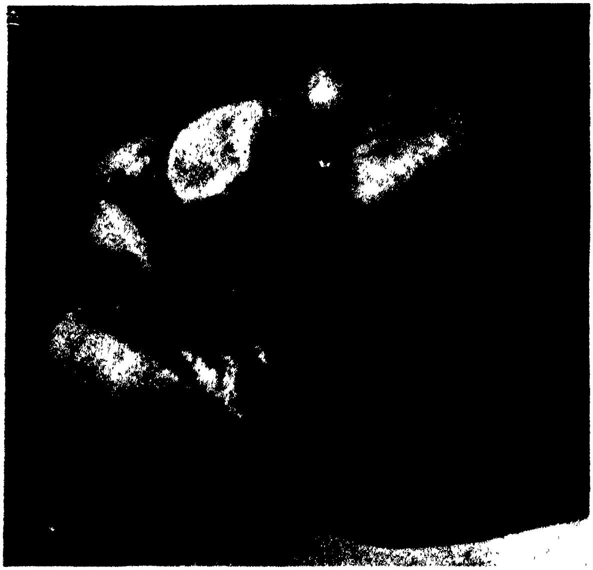


Fig. 118.—Ringworm of the foot.

Treatment.—The application of Whitfield's ointment, after the feet have been soaked in hot water, is recommended : salicylic acid 1, benzoic acid 1, coco-nut oil 12, soft paraffin 16 parts. This ointment must be persisted with for three weeks or more.

Rademacher (1943) recommended the following treatment, which has been found most effective during the present war : 25 per cent. sulphathiazole in talc is dusted on to the lesions daily. Definite improvement appears within forty-eight hours. A commercial preparation consists of 5 per cent. sulphathiazole in a bland ointment and has been found satisfactory. All infected areas should be covered with a film of the powder. The criterion of cure is the healing of all lesions and disappearance of adherent cutaneous débris. In refractory cases 10 per cent. of powdered sulphathiazole is made up with 2 per cent. salicylic acid ointment. The course of treatment lasts from two weeks to one month.

Other authorities favour azochloramide in triacetin, 1 in 500. This penetrates some distance into the tissues and thus enables the germicide —azochloramide—to extirpate the deeper filaments. This preparation N-N—dichloroazo-dicarbonamidine, is a complex chlorine compound, which liberates chlorine slowly.

A preparation which can also be recommended is *Merthiolate cream* (Eli Lilly & Co.) and also tincture of merthiolate, a solution of merthiolate in spirit, which sinks deep into the affected skin and thereby kills off the spores of the fungus.

For eczematous complications the toes should be separated by strips of gauze, and the foot should be covered with it and kept constantly wet with glycerine of lead subacetate, 1 oz., glycerine, 1 oz. and water to 1 pint. This lotion can be later replaced by Lassar's paste. If a staphylococcal infection is present, dressings of acriflavine, 1 in 20,000, should be applied.

As an after treatment Macleod recommended bathing or paddling in sea-water.

Infected patients should take careful precautions against the spread of the fungus, and should wear special slippers in the bathroom. Loofah soles and bath towels are recommended as they can be sterilized by washing.

As a measure against re-infection the patient may wear cotton toe-caps, which must be boiled, and he should also have a rubber bath-mat for exclusive personal use.

Ringworm of the Nails (*Tinea Unguium*)

This is a mycotic infection of the nails and is a comparatively common and extremely intractable condition in Europeans, especially in India and China ; it may last for twenty years or more. It may occur as an independent affection, or secondary to ringworm of the skin, scalp or beard, and is often found in association with tinea cruris. One or all of the nails of both hands and feet may be attacked. The fungus is a trichophyton, usually *Epidermophyton inguinale*.

The fungus first attacks the epidermis of the nail-bed and gradually invades the nail matrix. In doing so it causes considerable discoloration, ridging and fissuring of the nail itself, which becomes opaque, with a brittle, frayed edge. The fungus may pass from the skin over the nail-fold and in this manner reach the matrix.

Diagnosis.—The appearance of the affected nail is not sufficiently characteristic to be distinguished without microscopic examination. The disease is generally well advanced before it can be recognized. For microscopic diagnosis, scrapings of the nail are boiled in liquor potassæ, or left to soak for twenty-four hours. The scrapings themselves should be made as thin as possible with a piece of glass. The fungus can then be recognized in the softened nail débris, especially in small dark hæmorrhagic spots. The diseases liable to confusion with ringworm of the nails are *eczema, syphilis* and, especially, *psoriasis*.

Treatment.—In the early stages, when the lunule is attacked, t disease may be stamped out by softening the affected portion with soluti potash, and painting with tincture of iodine or with a 2 per cent. soluti of corrosive sublimate in alcohol, twice daily. When the nail is complet involved, cure is almost impossible save by extirpation or by avulsi The result is, however, disappointing, as the new nail usually becom infected in turn. After removal, the thickened nail-bed should be scrap and the matrix dressed with a parasitical ointment :

Acid. salicyl.	gr.xxx	(1·944 grm.)
Hydrarg. ammon. . . .	gr.xv	(0·097 grm.)
Vaseline	℥i	(31·1 grm.)

The shedding of the nails by application of X-rays is unsatisfacto Less severe cases are treated by softening the nail-plate by wearing rubb finger-stalls containing soft soap for a few days ; the softened nail is th scraped down as far as possible with glass, followed each time by t application of lint soaked in Sabouraud's iodine (iodine 5, potassium iodi 1, water 100), which should be kept in position by a loose rubber finger-sta

TINEA IMBRICATA

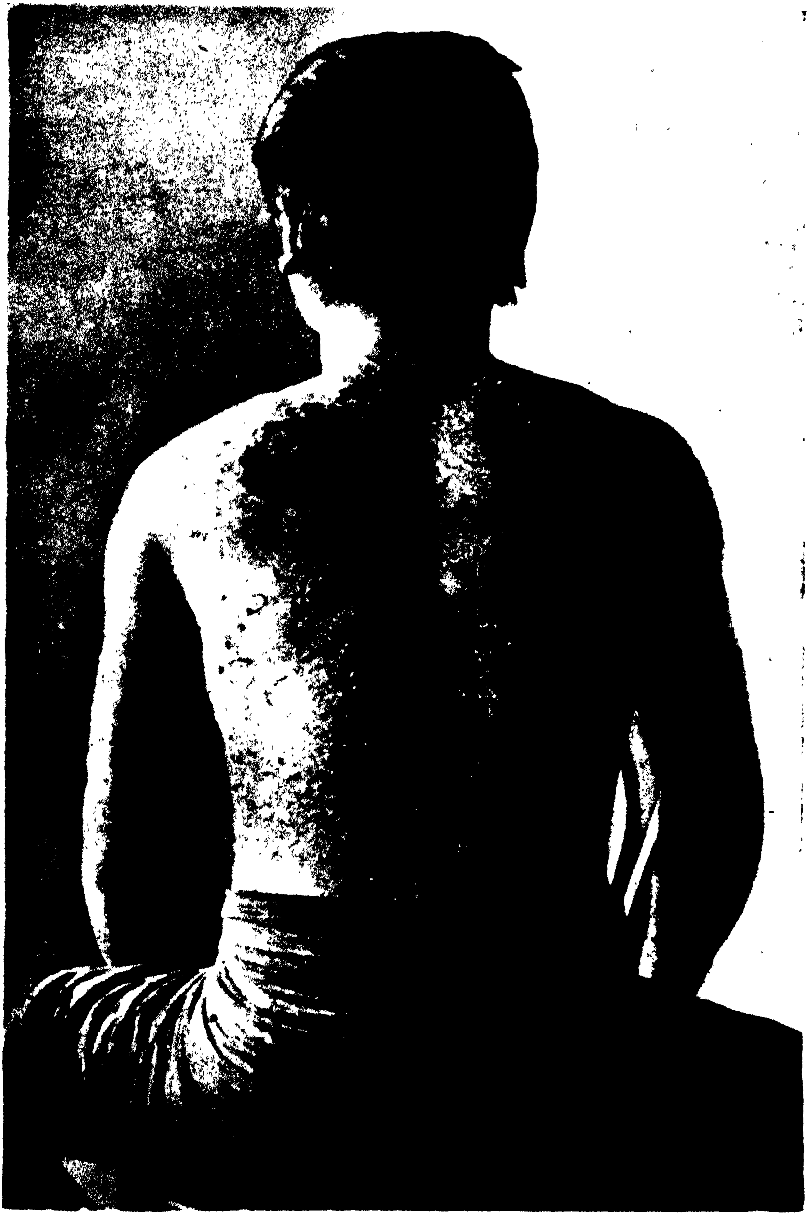
Synonym. Tokelau Ringworm.

Geographical distribution.—The affection is principally met in t Eastern Archipelago and in the islands of the South Pacific, where affects a large proportion of the population. It has been found to exte westwards as far as Burma, and northwards as far as Formosa and Fooch on the coast of China. Cases have been reported from Central Africa a the interior of Brazil. Once introduced, it spreads very rapidly in countri with a damp, equable climate and a temperature of 80–90° F. Very hi or very low temperatures and a dry atmosphere are inimical to its extensio

Ætiology.—On detaching a scale and placing it under the microscop after moistening with liquor potassæ, a trichophyton-like fungus can seen in enormous profusion. The parasite evidently lies between epiderm and rete, and by its abundance causes the former to peel up. As t fungus does not die out in the skin travelled over, it burrows under t young epithelium almost as soon as the latter is reproduced. Hence t peculiar concentric scaling and the persistence of the disease througho the area involved. When the scales are washed off by the vigorous u of soft soap and hot water, the surface of the skin is seen to be cover with brownish parallel lines—evidently the slightly pigmented fung proliferating and advancing under the young epidermis.

The parasite, said to be of two varieties, *Endodermophyton concentricum* a *E. indicum*, can be cultured by immersing the scales in alcohol for five to t minutes and then placing them, one scale to each tube, in glucose broth. Aft five or ten days the scales, if uncontaminated, are transferred to solid medi and growth takes place in three or four weeks.

Symptoms.—Tinea imbricata may at first be confined to one or tw spots on the surface of the body ; usually, in a short time it comes occupy a very large area. It does not generally affect the soles and palm although it may do so ; nor is the scalp a favourite site. Baker remark



TINEA IMBRICATA.

permission of Medical Department of Sarawak Government.)

PLATE XVIII

SALAR JUNG

PINTA.

(Photo : Dineen, San Francisco.)

PLATE XIX

that it avoids the crutch and the axillæ. With these exceptions it may, and commonly does, sweep over and keep its hold on almost the entire surface of the body, so that after a year or two a large part of the body is covered with the dry, tissue-paper-like scales, arranged in more or less confused systems of concentric parallel lines. This arrangement of the scales is absolutely characteristic of the disease (Plate XVIII).

An inoculation experiment readily explains the production of the scales, their concentric parallel arrangement, and the mode of extension of the patches. About ten days after the successful inoculation of a healthy skin with tinea imbricata, the epidermis at the seat of inoculation is seen to be very slightly raised and to have a brownish tinge. Presently the centre of this brownish patch—perhaps a quarter of an inch in diameter—gives way, and a ring of scaling epidermis, attached at the periphery, but free, ragged, and slightly elevated towards the centre of the spot, is formed. In a few days this ring of epidermis has extended so as to include a larger area.

The scales, if not broken by rubbing, may attain considerable length and breadth; but, of course, their dimensions are in some degree determined by the amount of friction to which they are subjected. Usually, they are largest between the shoulders—that is, where the patient has a difficulty in scratching himself. The lines of scales are from ⅛ to ½ in. apart.

Diagnosis.—From *ordinary ringworm*, tinea imbricata is easily distinguished by the absence of marked inflammation or congestion of the rings, by the abundance of the fungus, by the large size of the scales, by the concentric arrangement of the many rings or systems of rings, by the non-implication of the hair, and by the avoidance of crutch and axillæ. From *ichthyosis* it is distinguished by the concentric arrangement of the scaling, by the peripheral attachment of the scales, and by the presence of an abundance of fungus elements.

Treatment.—The best treatment for tinea imbricata in natives is the free application of linimentum iodi; its action is said to be increased by the addition of salicylic acid, 15 gr. to the ounce. Limited patches may be treated with chrysophanic acid ointment (20 gr. to the ounce), or by the more modern preparation, cignolin. Clothes should be boiled or burned.

Prophylaxis.—Daniels related that tinea imbricata is a comparatively rare disease in Tonga, and the natives attribute this to their custom of oiling the body with coco-nut oil. Since the Fijians adopted this practice the disease has become somewhat less prevalent among them. Personal cleanliness, and the immediate and active treatment of any scaling spot, should be carefully practised in the endemic countries. Amongst certain Central African tribes, it has never been observed in women, who oil their bodies, whereas the men, who do not adopt this custom, are subject to the disease.

In Tahiti the use of chrysophanic acid is now general among the natives; as a consequence, the disease is less prevalent there than it was only a few years ago.

VII. SPIROCHÆTAL SKIN DISEASE AND AFFECTIONS OF THE HAIRS

PINTA

Synonyms. Caraate ; Mal del Pinto.

Definition.—A spirochætal disease characterized by peculiar pigmented patches on the skin.

Geographical distribution.—Pinta occurs in certain districts in tropical America, especially along the river banks—in Mexico, Venezuela, Colombia, Bolivia, and in one or two places in Peru, Chile, Guatemala, Honduras, and Brazil.

Ætiology.—For many years this peculiar skin disease was regarded as due to parasitic fungi. Herrejon (1927) suggested that the pinta was produced by a spirochæte allied to that of syphilis and yaws. Armenteros and Triana in Cuba (1938) found this organism in the skin abrasions, and Blanco (1938) obtained it by lymph gland puncture. To this spirochæte the name of *S. herrejoni* was given. This discovery was confirmed by Blanco (1938) in Mexico, by Iriate in Venezuela (1939) and by Leon in Ecuador, who found the organisms especially abundant in the early papules. Brumpt (1939) proposed the name *Spirochæta* (*Treponema*) *carateum*, but the correct terminology should be *S. herrejoni*, which has priority.

This spirochæte, in measurement as well as in appearance (by dark-ground illumination), is closely allied to *S. pallida*. When first isolated it is very active, but its motility decreases in about twenty minutes. It is 12 to 18 μ in length, and easily stained by silver impregnation and by Giemsa stain. It is readily dissolved by saponin and dies in a short time in bile. (Fig. 119).

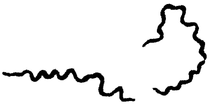


Fig. 119. Spirochæta herrejoni (carateum). (*After Leon y Blanco.*)

Varela claimed that *S. herrejoni* has certain differences from most other spirochætes. When stained by Giemsa it has a flexible cylindrical form with pointed ends. The turns are 0·6–1 μ in width, 0·4–0·5 μ deep and 9–10 in number.

Animal inoculations.—The Venezuela Commission reported that inoculations in guineapigs, rabbits and rats were without result, but Sænz (1940) inoculated the cornea and testes of rabbits with pinta tissues and stated that keratitis and epididymitis, resembling those of syphilis, were produced.

Human Inoculations.—Blanco (1940) demonstrated, by inoculation into volunteers that the disease is infectious and may be easily transmitted when a small amount of serum from a pinta lesion is injected. In syphilitic patients an initial papule developed, but the secondary eruption was atypical. Positive Wassermann reactions were obtained, but not before the appearance of the secondary eruption. The primary lesion differs from that of syphilis or yaws in that it is always closed and does not ulcerate. Experimental inoculations showed that previous syphilis does not give absolute immunity to pinta.

Pathology.—The spirochætes are chiefly located in the Malpighian cells, especially in small areas of acanthosis in the epidermis. A greater involvement of the corium has been described in pinta than in yaws, but much less than in syphilis. Spirochætes may be demonstrated in lymph obtained from glands near the lesions. The hair follicles and portions of the sweat glands are surrounded by inflammatory cells. The pigmentary function is specially affected in pinta, and scanty pigment granules may be seen inside the cells of the stratum germinativum ; they are also present in other cells of the Malpighian layer and in the melanophores of the dermis.

Symptoms.—The incubation period in experimental inoculations varies from 7–20 days, by which time an initial papule appears. This extends peripherally as a squamous, reddish patch, reaching a diameter of 1 cm. in a month, and then continues to spread peripherally. Secondary lesions appear in crops around the primary papule, spreading to other parts in about five months. Progressive hyperpigmentation is then observed ; later still, depigmentation, which gives rise to various colours, or vitiliginous spots, ranging over the body. The colour of the lesions in order of frequency appears to be blue, white, mixed, lead-coloured, violet, black, red or yellow. The spots vary in size and in shape : round, oval or irregular. They are not elevated, but are always strikingly visible (Plate XIX)

In natural infections the primary lesion is usually on an exposed part, particularly the legs and feet and arms, extending to the hands and face. According to Blanco, the initial lesion is never seen on the palms, or on the trunk. Modern observers divide the disease into three distinct stages, showing different clinical, serological and immunological features.

The primary stage occupies the period when the initial lesion is present and lasts from five months to one year. The secondary stage is characterized by skin lesions or papules which are rapidly converted into erythematous squamous lesions (named *pintids*) and ensues five months to one year from the time of infection. In the tertiary, or *dyschromic*, stage there are achromic or pigmentary spots, erythema, keratoderma and superficial atrophy. Super-infections may be produced by inoculations at this stage. Hyperkeratosis of palms and soles, as in yaws, are to be regarded as late manifestations. Eosinophilia and an increase of basophil cells occur in a high percentage of cases.

The exact relationship of pinta to syphilis is further complicated by the fact that Sænz in Cuba found aortitis, aneurysm and enlargement of the diameter of the heart and valvular lesions in 23·3 per cent. The association of this skin spirochætosis with visceral syphilis is of course conceivable.

Diagnosis.—The characteristic spirochætes are present in the lesions, but obviously it is impossible to differentiate them in their morphology from *S. pallida* or *S. pertenuis*. Pinta is often associated with syphilis and yaws lesions, such as juxta-articular nodules. Sænz found changes in the cerebro-spinal fluid in 10 per cent. (increased globulin content and colloidal gold curve).

Depigmented, or vitiliginous areas are common in tertiary yaws and syphilitic lesions in the coloured races to which pinta is almost entirely limited. It is obvious that many other skin diseases have in the past been confused with pinta. Apparently too many examinations have been made for the presence of fungi and micro-organisms without proper cleansing and disinfection of the skin.

Differential diagnosis has to be made from leprosy, yaws, syphilis, erythrasma, pityriasis versicolor and other epiphytic skin diseases, and also from plain vitiligo or leucoderma.

Treatment.—The modern treatment for pinta is neosalvarsan and bismuth preparations, as described for yaws. The superficial skin lesions yield rapidly to salvarsan, but the atrophic vitiliginous spots remain unaffected, as in yaws. The Wassermann reaction in a proportion of cases remains positive after disappearance of the lesions.

TRICHOSPOROSIS

Synonym. Piedra.

This peculiar disease of the hair is very common in certain districts of Brazil, Colombia and British Guiana. It was thought to be confined to the inhabitants of these countries, where a considerable proportion (both male and female, and apparently of all races) are affected, but it has also been found in West Borneo by Kuypers. It has been observed on the eyelashes, beard, and scalp. It is commoner in native women than in men.

The hairs are dotted over at irregular intervals with numerous (1 to 10 or more in a hair 60 cm. in length) minute, gritty nodosities, which feel like sand grains—hence "piedra," sandy. These, barely visible to the naked eye, are distinctly perceptible to the touch when the hair is drawn between finger and thumb. The affected hairs are bent and twisted, and tend to produce matting and knotting. The little nodosities are very firm, but not so hard as the name piedra (a stone) would indicate, being easily cut through with a sharp knife or scissors. They are paler than the hair which they surround, or partly surround, like a sheath. They are situated in the extrafollicular portion and vary from one to ten or more. When a comb is drawn through the hair, a sort of crepitation is produced, doubtless by friction against the hard particles.

In Brazil piedra is known as far as Bahia; Horta published a monograph there which remains a model of precise observation.

Ætiology.—Under the microscope the excrescences are found to consist of a number of spore-like bodies, *Trichosporon giganteum*, easily made apparent by soaking the hair in liquor potassæ after washing in ether. Langeron has suggested that the correct name for this parasite should be *Piedra hortai* as he considers that it is probably an epiphyte analogous to certain fungi which grow on the leaves in the forests of Central America. The spores are twins, the size of trichophyton spores, and remarkably refringent, and are polyhedral from mutual pressure. Together they form a sort of tessellated mosaic, the elements of which seem to be held together by a greenish soluble cement in which a number of minute bacteria-like rods are incorporated. The shaft of the hair—not eroded or affected in any way—can be seen intact through the encrusting fungus. *T. giganteum* is easily cultivated on ordinary media. It liquefies gelatin in ten or twelve days. The smallest spores measure 2–5μ, the largest up to 12μ. Piedra is supposed by some to be induced by the mucilaginous hair applications in vogue among the Colombians.

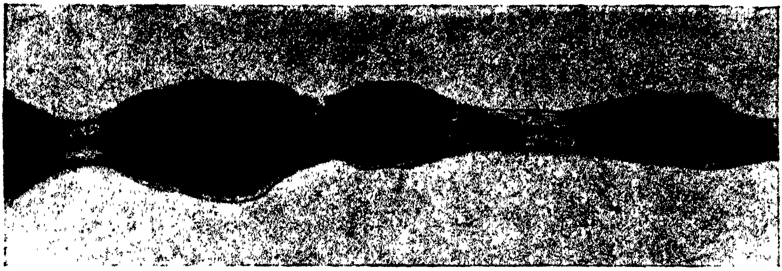


Fig. 120.—Human hair (magnified) affected with *Trichosporon beigeli.*

Diagnosis.—Although Juhel-Rénoy has given to piedra the name "trichomycose nodulaire," the conditions must not be confounded with trichomycosis nodosa, which is a different affection and common enough on the axillary, scrotal and face hair in Europe and elsewhere. Neither must it be confounded with trichorexis nodosa, a non-parasitic disease of the hair-shaft, which is split up at different points into brush-like bundles of fibres, and is thus easily fractured ; nor with moniliform hair, a congenital, hereditary, and non-parasitic condition.

Treatment.– Cleanliness, the free use of soap, and the application of some epiphyticide should suffice for cure ; but should such means fail, doubtless shaving the scalp would be effectual.

TRICHOMYCOSIS

Synonyms. Trichonocardiasis ; Trichomycosis nodosa.

Trichomycosis is a fungous disease of the hair, found in Central Africa and Asia, which in many ways resembles piedra. It may produce skin irritation and stain the clothes. The shafts of the hairs, more especially those in the axilla, are attacked. The parasite is *Trichosporon beigeli* (Rabenhorst, 1867). This has been thoroughly studied by P. Vuillemin (1902). On the hairs it produces irregular nodosities containing the fungus elements, each 3μ to 5μ in length. In cultures, mycelial formation takes place, composed of arthrospores, giving rise to blastospores, and in older cultures to ascospores. The fungus is easily cultivated on Sabouraud's medium, or beer-wort.

This fungus, which was first discovered in London by Beigel in 1862, has been found occasionally in Europe, and is quite common in Japan. It may attack the beard and moustache, which may become matted together so that they cannot be combed out. The affected part emits a peculiar odour, as in the Editor's case from which the illustrations are taken. (Figs. 120, 121.) The hairs have a beaded or nodular appearance and the deposit may vary considerably in colour. The disease may spread to the skin and cause severe intertrigo.

Microscopically, the lesions consist of a mass of polygonal cells, yellowish-green to brown, with a definite cell-wall. The cells of a mycelial thread are separated from one another by thick black cell-walls, between which there is little intercellular substance.

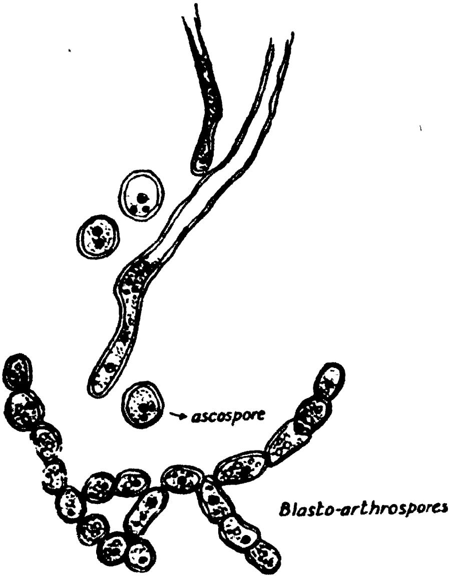


Fig. 121.—Fungus elements of *T. beigeli*.

Treatment. — The affected hair should be bathed twice daily with a lotion consisting of 1 dr. of formalin to 6 oz. of rectified spirit, reinforced by 2 per cent. sulphur ointment. The affected surrounding skin should be rubbed with mercurial ointment.

VIII. SKIN DISEASES CAUSED BY ANIMALS

THE CHIGGER, OR SANDFLEA

This insect, formerly confined to the tropical parts of America (30° N. to 30° S.) and to the West Indies, appeared on the West Coast of Africa for the first time about the year 1872. Since that date it has spread all over the tropical parts of that continent, and even to some of the adjacent islands—Madagascar, for example. As a cause of suffering, invaliding, and indirectly of death from secondary infections, it is an insect of some importance. It is now extremely prevalent on the East Coast of Africa, and is causing a large amount of invaliding among the Indian coolies there by whom it has been introduced into India as far east as Karachi, but in no other part.

The chigger (*Tunga penetrans*) is not unlike the common flea either in appearance or, with one exception, in habit. It is somewhat smaller (1 mm.), the head being proportionately larger and the abdomen deeper than in the flea. It is red or reddish brown. Like the flea, its favourite haunt is dry, sandy soil, the dust and ashes in badly kept native huts, the stables of cattle, poultry pens, and the like. It greedily attacks all warm-blooded animals, including birds and man. Until impregnated, the female, like the male, is free, feeding intermittently as opportunity offers. As soon as she becomes impregnated she burrows diagonally into the skin of the first warm-blooded animal she encounters where, being well nourished by the blood, she proceeds to ovulation. By the end of this process her abdomen, in consequence of the growth of the eggs it contains, has attained the size of a small pea. (Figs. 122, 123.) As seen in Fig. 123, the chigger within the epidermis enters the stratum lucidum;

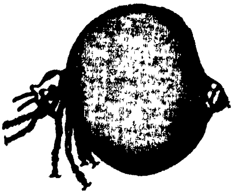


Fig. 122.—Chigger, impregnated female. × 10. (*Blanchard.*)

which it invades and pushes before it. The epithelial layer becomes attenuated. The parasite becomes anchored in the corium by means of chitinous excresences which stick out into the surrounding tissues. The first anterior and the two posterior segments do not participate in the enlargement, the latter acting as a plug to the little hole made by the flea on entering the skin. When the eggs are mature they are expelled by strands of muscular fibres which intersect the abdomen. They fall on the ground and, according to Hicks, the larva hatches on the third or fourth day; the first moult occurs on the fifth to eighth day and preparation for pupation on the sixth to seventeenth days. The larva pupates at the same time, and the imago usually emerges about the seventeenth day. (*See also* Appendix p. 996).

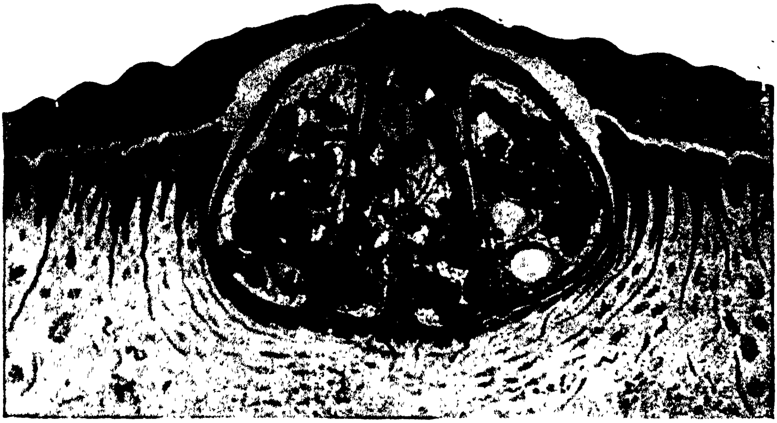


Fig. 123.—Section of female chigger in the stratum lucidum of the skin.
(*Fülleborn, Arch. für Schiffs-und Tropenhyg.*)

During her gestation the chigger causes a considerable amount of irritation. In consequence of this, pus may form around her distended abdomen, which now raises the inflamed integument into a pea-like elevation. After the eggs are laid (according to some, before this process) the superjacent skin ulcerates, and the chigger is expelled, leaving a small sore which may be infected by some pathogenic micro-organism, such as the bacterium of phagedæna or of tetanus, with grave consequences (Fig. 124.)

The chigger is not a good jumper and therefore she seldom attacks the skin *above* the dorsum of the foot.

The soles (Fig. 125), the skin between the toes, and that at the roots of the nails are favourite situations. Other parts of the body are by no means exempt; the scrotum, the penis, the skin around the anus, the thighs, and even the hands and face, are often attacked. Usually only one or two chiggers are found at a time; occasionally they are present in hundreds, the little pits left after their extraction, or expulsion, being sometimes so closely set that parts of the surface may look like a honeycomb.

Ulceration is common, and may follow removal of the chigger or natural extrusion of the egg-sac. The ulcer commences as a tiny pit and, as it extends, the sloping edge may develop into septic ulcer. It remains more or less circular in outline, except under the nail or nail margin, where the outline is more irregular and a pocket of pus forms underneath it. Chronic absorption of pus may lead to thrombophlebitis.

Treatment.—In chigger regions the houses, particularly the ground floors, must be frequently swept and accumulations of dust and débris prevented. The housing of cattle, pigs, and poultry demands the same precautions. The floors should often be sprinkled with carbolic water, pyrethrum powder, or similar insecticide, and walking bare-footed must be avoided. A daily bath must be taken, and any chiggers that may have fastened themselves on the skin at once removed. They may be killed by pricking them with a needle, or by the application of chloroform, turpentine, mercurial ointment, or similar means, after which they are expelled by ulceration. The best treatment, however, is not to wait for ulceration, but to enlarge the orifice of entrance with a sharp, clean needle and neatly to enucleate the insect entire. Some native women, from long practice, are experts at this little operation. The part must be dressed antiseptically and protected until healed. Europeans living in an endemic district should wear high boots. A daily inspection of the feet, especially under the nails, is advisable. Should any black dot be discovered, the chigger should at once be removed.

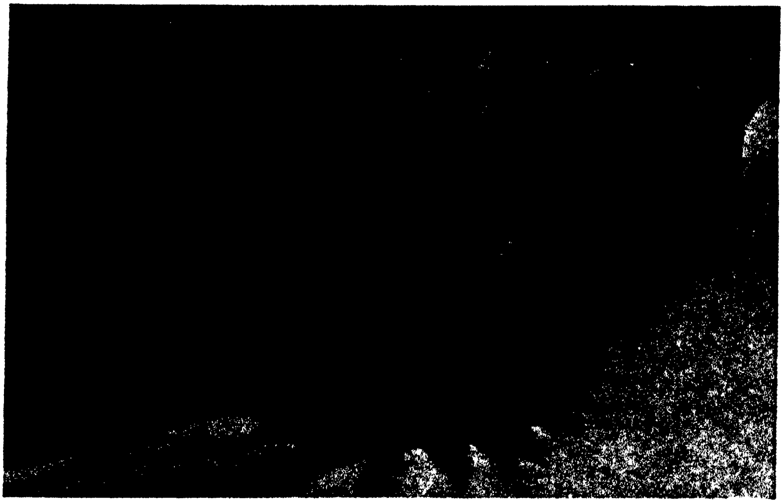


Fig. 124.—Septic lesions of foot caused by chiggers.

Prophylaxis.—If avoidable, camps should not be formed in chigger-infested spots or in the neighbourhood of native villages. The camping-ground should be swept or, if necessary, fired ; the floors of huts and tents may be sprayed with insecticides and naphthaline, and native tobacco dusted inside boots or shoes. Balfour recommended that the feet be rubbed thoroughly with a mixture consisting of 5 drops of lysol, or liq. cresoli sap., in 1 oz. of vaseline. Special attention should be paid to the interdigital clefts. Pigs should not be kept in the vicinity of dwelling-houses, as these animals are severely attacked by chiggers.

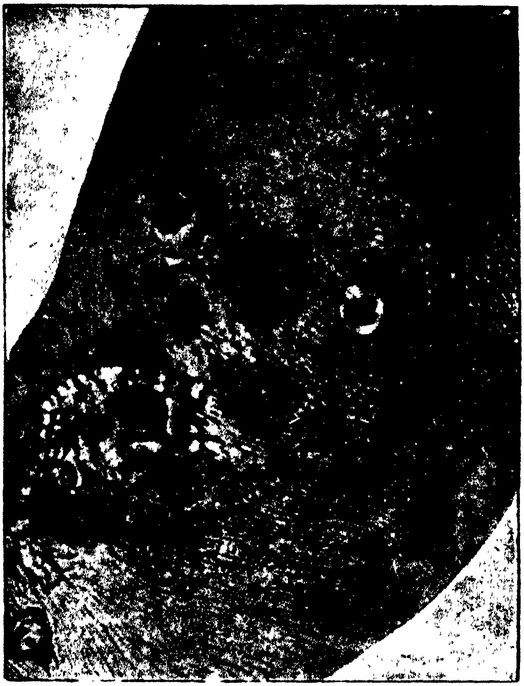


Fig. 125.—Chiggers in sole of foot. (*Dr. C. W. Daniels.*)

Acarine Dermatosis

Several forms of mites inhabiting sugar, grain, or copra may live as

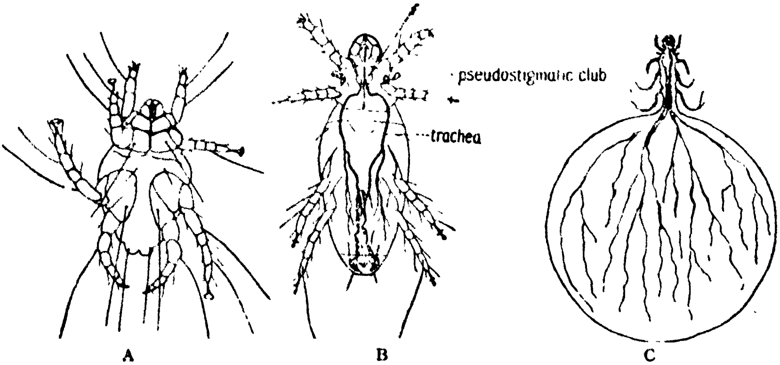


Fig. 126.—*Pediculoides ventricosus.* × 80. (*After Alcock.*)

A, Male; B, adult female; C, pregnant female with brood-sac.

temporary parasites on the skin of man, and set up an intense irritation not unlike that produced by scabies. One of the most familiar of these is "grocer's itch," set up by mites of the genus *Glycophagus*, which are common in raw sugar and cause an erythematous rash. Among the copra workers in Ceylon and the Pacific islands a similar skin affection is due to *Tyroglyphus*. "Grain itch," an urticarial and papular eruption of the exposed parts of the body, is caused by *Pediculoides ventricosus* (Fig. 126, A, B, C) in those who handle grain, cotton-seeds, or beans. These mites give rise to a severe pruritus. Preventive treatment consists in the application of 5 per cent. beta-naphthol ointment, and dilute carbolic acid to kill the mites.

Section VIII.—LOCAL DISEASES

CHAPTER XL

TROPICAL PYOMYOSITIS—RHINOSPORIDIOSIS—RHINOSCLEROMA—AINHUM—BIG HEEL—ONYALAI—CHIUFA—TROPICAL ENSINOPHILIA

I. Tropical Pyomyositis

Synonyms. Myositis Purulenta Tropica; Tropical Myositis; "Bung-pagga" (Patton).

History and geographical distribution.—In 1912 H. H. Scott described this disease in Jamaica. Deep intramuscular abscesses were associated with pyrexia, and a striking feature was the hard swellings set up by enormous collections of serous fluid. A small bacillus was isolated, which was named *B. serofaciens.*

In the same year Külz found intramuscular abscesses very common in the Cameroons; and in Duala, in 1907–1908, out of 386 natives, 18 were operated on for intramuscular abscesses, and out of 86 Europeans, 5 were thus treated. In natives abscesses were multiple; in Europeans usually single, and they varied in size up to that of a hen's egg. He believed that they were secondary to *Loa loa* infection.

In 1913, Wise and Minnett in British Guiana described what was obviously the same condition, and they failed to find remains of adult filariæ (*Wuchereria bancrofti*) in the pus, though filaria embryos were discovered in seven. Recurrence of abscesses in the same patient was a feature of the disease. In most instances streptococci were isolated from the pus.

Ziemann (1913) described an exactly similar form of intramuscular suppuration in New Guinea, and claimed that already, in 1904, he recognized the disease as one *sui generis* as distinct from suppuration with filariasis. In 1917, E. L. Walker reported upon cases from Brazil. Commes in 1918 met it in French West Africa, where it had previously been noted by Bouffard. In 1922, Laigret and Lefrou, in French Equatorial Africa, remarked upon the deep chocolate colour of the pus, almost resembling liver-pus. Tanon and Jamot (1926) found it common in the Cameroons during the 1914–18 war, when it was known as "*lambo lambo.*" Summaries of our knowledge on this subject have been made by Appel (1921) from the German, and Connal (1930) from the British view-point, and Gibler (1922) gave further details of pyomyositis in Northern Australia and Papua, and James in the Solomon Islands. Van Steenis (1931) recognized the same disease in Java. P. A. Buxton (1928) published a very complete account of myositis as he observed it in Samoa, and was convinced on ætiological grounds that myositis is distinct from the deep suppuration sometimes observed in filariasis. It is of considerable importance in Samoa, and was observed in Europeans, Samoans, half-castes, Chinese, and Melanesians. He found that pulmonary complications were not infrequent, abscesses were invariably intramuscular, suppurative and non-suppurative lesions were common, while *Staphylococcus aureus* was the organism responsible. Grace and Grace (1931) investigated an outbreak, which amounted to an epidemic, in the island of St. Kitts. The outbreak affected more than 300 individuals, with a death-rate of 10 per cent. Some cases resembled septicæmia. The Editor has treated cases in Europeans, Chinese, Japanese, Indians, Negroes and Polynesians.

Ætiology.—The infection was regarded by Pawan as secondary streptococcal and staphylococcal infection in filaria-infected subjects. Grace thought that the causal organism was a hæmolytic streptococcus derived from the throat. Von Bormann thought that the organism was a hæmolytic staphylococcus, usually *S. aureus*, less commonly *S. albus*. Erasmus in East Africa found the former most frequently. In the Editor's experience these two organisms are responsible, though occasionally *Streptococcus pyogenes* is found.

The site of entry is uncertain, but dissemination appears to take place by the bloodstream, for the lymphatics and lymph glands may show no sign of inflammation.

Associated infections.—Pyomyositis is more apt to occur in persons who are debilitated as the result of some other longstanding infection. In the Editor's experience this has been either ancylostomiasis, malaria, and, in a proportion, syphilis. In his series of cases the Wassermann reaction was positive in 50 per cent. One of the chief aims of treatment should be the eradication of these concomitant infections, and, wherever necessary, antisyphilitic treatment with salvarsan and bismuth should be instituted.

Symptoms.—Several types may be distinguished.

Acute non-suppurative stage.—An indurated, tender, ill-defined mass can be felt in the affected muscles where the patient complains of pain. There is usually slight pyrexia, with inflammatory reaction over the neighbouring tissues and pitting œdema. On incision the tissues are œdematous, whilst the regional lymph glands are usually enlarged and tender.

Acute suppurative stage.—The clinical features are those of a deep-seated abscess, and, on incision, large collections of pus in the affected muscles are evacuated. The abscess cavity is loculated, requiring a wide incision and the breaking down of septa formed of dense indurated muscle, or fibrous tissue. The numerous sloughs in the cavity are characteristic. These abscesses occur in widely separated sites : in the thigh muscles, pectoralis major, serratus magnus, latissimus dorsi, gastrocnemius, flexor muscles of arm and iliopsoas and internal oblique. Generalised septicæmia may result.

Chronic abscesses have been recorded in the adductor magnus.

Diagnosis.—The diagnosis of pyomyositis should not present any great difficulty, but it has to be differentiated from gummatous suppuration, filarial abscesses, glanders, melioidosis, rheumatic nodules and swelling, osteitis of femur, cold abscesses of sacro-iliac joint, septic mastitis, perinephric abscess and fibrosarcoma.

Treatment.—The course of events is well illustrated by the case of a European from British Guiana who was treated in 1931. The illness lasted over one year and began as external boils, mostly in the feet and arms. Soon he suffered from febrile attacks, associated with rheumatic-like stiffness of the muscles. Small hard nodules were noted on the leg, thigh, pectoral and submaxillary regions. Stiffness of the legs was caused by diffuse indurated swellings in the extensor muscles, which were due to serous infiltration. During the seven months he was under the Editor's care no less than fifteen inflammatory swellings appeared in various parts of the body, associated with stiffness, pain, and pyrexia. The extensor muscles of the thigh were the seat of several large abscesses. The Wassermann reaction was positive. There was a moderate leucocytosis of 15,000–19,000. From time to time inflammatory periosteal nodules appeared which could be demonstrated by X-rays. There was synovitis of both knee-joints. Eventually, a large abscess appeared in the right pectoralis major muscle, leading to partial necrosis of the eighth rib, which had to be resected. The organism responsible was *Staphylococcus aureus.* The patient eventually recovered after eight surgical operations and prolonged antisyphilitic treatment with bismuth and neosalvarsan. Combined treatment with a vaccine of *Staphylococcus pyogenes aureus* was fairly successful. Earle thinks that surgical treatment is best, combined with intensive sulphonamide therapy, especially sulphapyridine and sulphathiazole.

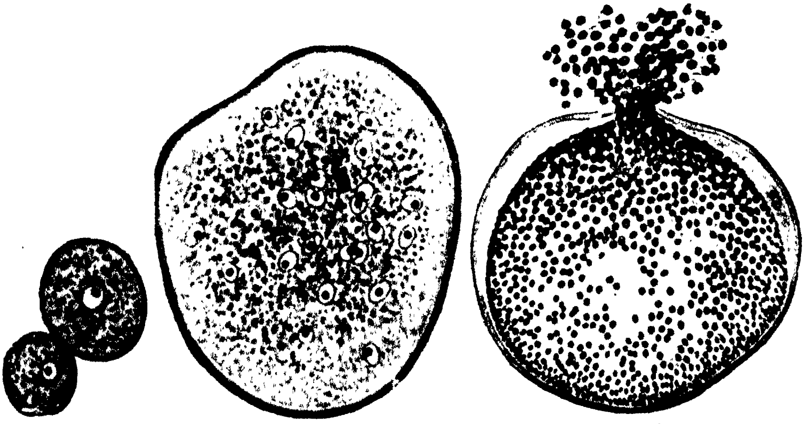
II. RHINOSPORIDIOSIS

Definition.—A disease due to a yeast-like organism, *Rhinosporidium seeberi,* which infects the mucous membrane of the nose, producing nasal polypi and tumours on the cheek, conjunctiva, lachrymal sac and uvula.

History.—*R. seeberi* was first described in Argentina (1896), and considered to be a protozoon allied to *Coccidium.* Subsequently it was found in nasal polypi by O'Kinealy in 1903, when the organism was described by Minchin and Fantham. Ashworth (1923) thought that the organism is probably a yeast, or phycomycete.

This parasite has now been recorded from India, Ceylon, Argentina, Uganda (Mowat and Hennesey, 1941), and the United States.

Ætiology.—*Rhinosporidium seeberi* (Wernicke, 1903) is a spherical or oval non-motile organism which occurs in polypoid growths, usually lying between the connective-tissue cells. The earliest stages are about 6 μ in diameter, with a chitinous envelope, vacuolated cytoplasm, and vesicular nucleus containing a karyosome (Fig. 127, A, B). When fully-grown, the cyst, or sporangium, may measure 0·25–3 mm. in diameter, but when half-grown the nucleus commences to divide by binary fission, until thousands are produced, of which the majority become daughter-spores, though a considerable proportion remain unchanged. The fully-formed sporangium (Fig. 127, C) finally bursts and discharges the spores, which are enclosed in chitinous envelopes; they then



A × 400 B × 400 C × 180

Fig. 127—*Rhinosporidium seeberi.* (*After Ashworth; by permission of Roy. Soc. of Edin.*)

A, Trophic stages. B, Section of a stage with 64 nuclei, 24 of which lie in this section. C, Sporangium from which spores are being discharged, accompanied by mucoid substance, through a wide orifice. The first spores to issue (those near the opening) are followed by the central spores. The peripheral spores lie in a fairly firm mucoid matrix. Stretching of the envelope, due to growth of the sporangium, has not only reduced its thickness, but has almost caused the disappearance of the thickened annulus round the pore.

spread into the connective tissues *via* the lymph channels, and on reaching suitable spots the trophic stage at once begins and the cycle is repeated.

Attempts at cultivation proved partially successful in Ashworth's hands, and multiplication of the spores took place, but slowly, on Sabouraud's medium.

The mode of transmission of this parasite is undetermined, but the occurrence of a closely related organism, *R. equi*, in the nasal cavities of the horse is suggestive.

Treatment consists in removing the polypi from the nares by a wire snare. Medical treatment does not appear to be indicated, although Wright reported that the tumours disappear after intravenous injections of tartar emetic. Allen (1936) used neostibosan though it is not always effective. A popular native remedy is a snuff composed of tobacco leaves and lime.

Fig. 128.—Rhinoscleroma of two years' duration in an Egyptian woman.
(*Dr. H. K. Giffen.*)

III. RHINOSCLEROMA

Rhinoscleroma (*Scleroma respiratorium*) (Fig. 128) is a well-marked disease in all its aspects, pathological or bacteriological. It has a world-wide distribution, but at the present day is much commoner in the Tropics than elsewhere. It takes the form of spontaneous, painless, and exceedingly chronic inflammatory growths occurring at any place in the respiratory passages from the nostrils to the hilum of the lung. Gross deformity of the nose, or narrowing or distortion of the respiratory passages results. Sometimes there is perforation of the nasal septum with total destruction of the uvula. The process extends along the respiratory passages with little change in the surrounding tissues; on the whole, it tends to form metastases with enlargement of the neighbouring lymphatic glands, but, in spite of this, the general health and condition remain unaffected.

Geographical distribution.—Rhinoscleroma is spread over widely distributed regions in special nests, or foci, but occurs all over the world. The most extensive region is in Eastern Europe, in Hungary, Poland, the Ukraine and the northern shores of the Black Sea and Caspian. Other foci have been noted at Tomsk in Siberia, in Turkestan, Bengal, Java, Sumatra, central and southern France, Morocco, Egypt, North America (in New England states), Cuba, Mexico, Panama, Colombia, Brazil, Peru, and Chile.

Ætiology.—The cause of rhinoscleroma is undoubtedly the *Bacterium* (*Klebsiella*) *rhinoscleromatis* described by V. Frisch in 1882. It is closely related to *Bact. pneumoniæ*, and is usually Gram-negative. It is easily cultivated, and forms knob-like colonies on gelatin or agar, greyish on the whole, and less conspicuous than *B. pneumoniæ*. It usually coagulates milk, and forms acid freely with lactose. In sections, it is found in hard fibrotic swellings in the nose, scattered throughout the mucosa and submucosa. It has so far been found impossible to reproduce the lesions by inoculation, either in man or animals. In fact, it exhibits a very low order of pathogenicity for laboratory animals, with the exception of mice. It has to be differentiated from other encapsulated pneumococcus-like organisms in the nose.

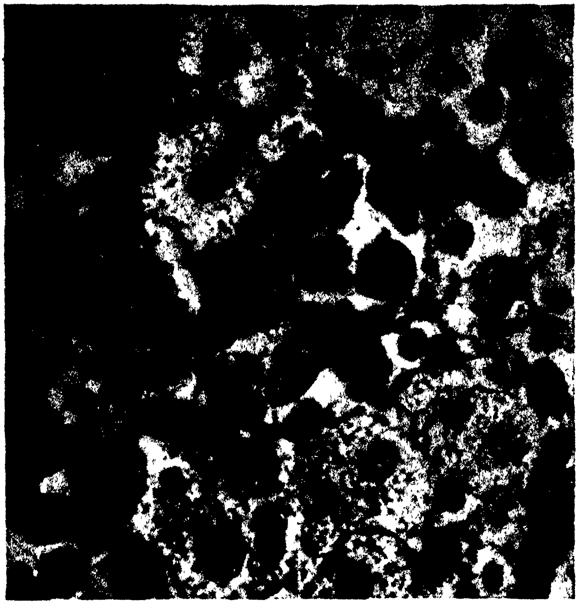


Fig. 129.—Rhinoscleroma: Photomicrograph of tissue, showing Mikulicz cells and general histological picture. (*Dr. H. K. Giffen.*)

Pathology.—Rhinoscleroma is characterized by a peculiar form of plasma-cell infiltration of great density, and by gaps or "fat-cells," which are found to consist of swollen cells with foamy cytoplasm ("foam-cells" or " Mikulicz cells ") (Fig. 129). Very frequently, also, there are hyaline-drops or Gram-positive " Russell's bodies," which occur in all kinds of degenerative tissues, and are probably derived from the plasma cells. The rhinoscleroma nodule is known as plasmoma (Unna) ; it never breaks down, but becomes progressively sclerosed.

Treatment. —The treatment is mainly by plastic operation to remove the unsightly outgrowths.

Various other methods, the most important of which is X-ray therapy, have been tried. Intravenous injection of tartar emetic, as in bilharziasis or ulcerating granuloma, has been advocated by some. It is a curious fact that complicating febrile diseases, such as erysipelas, typhoid or typhus fever, may cause healing of rhinoscleromatous growths. This has led to a trial of inoculated malaria or protein-shock therapy, with encouraging results.

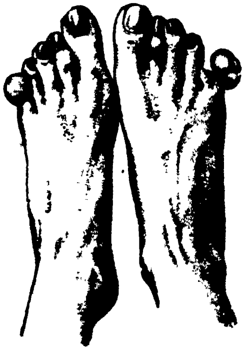


Fig. 130.—Ainhum.

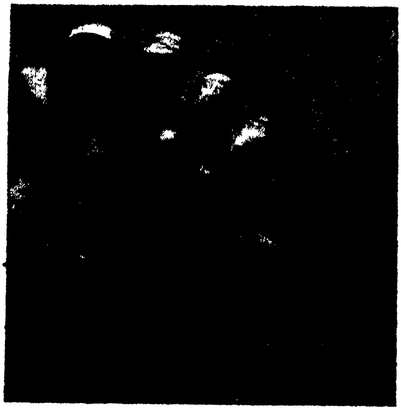


Fig. 131.—Ainhum at its height.
(*Dr. A. B. Filho.*)

IV. AINHUM

This is a very peculiar disease affecting the toes, particularly the little toes, of negroes, East Indians and other dark-skinned races, both in the Old and the New World. The name, derived from the Nago dialect, means " to saw or cut."

Symptoms.—The disease commences as a narrow groove in the skin, almost invariably on the inner and plantar side of the root of the little toe. It may occur in one foot only, or in both feet simultaneously, or it may affect one foot after the other. The groove, once started, deepens and extends gradually round the whole circumference of the toe. As it deepens—perhaps though not necessarily, with ulceration—the distal portion of the toe is apt to swell to a considerable size, as if constricted by a ligature (Figs. 130, 131). There is little or no pain, although there may be inconvenience from the liability to injury to which the dangling and now everted toe is exposed. In the course of years the groove slowly deepens, and finally the toe drops off, or is amputated. The groove may or may not correspond with a joint. In rare instances, after the two distal phalanges have dropped off, or been amputated, the disease recurs in the stump, and the proximal phalanx in its turn is thrown off. Of the other toes, the fourth is the one which is most frequently affected; very rarely is the third, second or great toe attacked. In the Army Medical Museum at Washington, U.S.A., there is a wax model representing a case of this or a similar affection, in which all the toes had been thrown off and the disease was making progress in the leg.

Occasionaly, the terminal phalanx of the fifth digit of the hand has been affected.

Ainhum is very rare in women or children, being most common in adult males. It runs its course in from one to ten or even more years.

On section, it is found as a rule, though not invariably, that the panniculus adiposus of the affected toe is much hypertrophied, that the bone is infiltrated with fatty matter, and that the other tissues are correspondingly degenerated. Sometimes the bone is thinned, or even altogether absorbed. At the seat of constriction a line of hypertrophy of the epithelial layers, and of atrophy of the papillary layer of the skin, together with a band of fibrous tissue, more or less intimately connected with the derma, surrounds, in whole or in part, the narrow pedicle.

Treatment.—It has been suggested that division of the constricting fibrous band would delay the evolution of the disease. In the early stage this might be tried. When troublesome, the affected toe should be amputated. It is said that the application of salicylic ointment delays the process in the earlier stages (Moreira).

V. Big Heel, or Endemic Hypertrophy of the Os Calcis

Maclean described a peculiar form of enlargement of the os calcis which he observed at Kaziankor, Gold Coast, among Fantis and Kroos. The disease begins somewhat suddenly, being preceded by fever, and attended by pain and tenderness which reach their maximum in about a month, gradually diminishing during the succeeding one or two months. Concurrently with the pain there is a swelling of the external surface of the os calcis, rarely of the other tarsal bones.

Maxwell reported a similar condition in natives of Formosa. As in Maclean's cases, the patients were young adults from twenty to twenty-five years of age.

VI. Onyalai (Essential Thrombocytopenia)

Under this title Massey and, later, Wellman (1904) originally described a peculiar disease occurring among the natives of Portuguese West Africa. Since then it has been recognized in East Africa, Tanganyika, on the Congo, and in Northern Rhodesia, where it is known as "Chilopa," "Kafindo," or "Akembe," (bleeding disease—Wallace). It is not usually seen outside Africa, though Preston Maxwell in 1901 described a somewhat similar condition in the Fokien region of South China. It is characterized by formation of a number of vesicles, distended with blood, from ½ to ¾ in. in diameter, on the hard palate and on the inside of the cheeks. Some of them are umbilicated. They differ from ordinary blood blisters by the presence of numerous trabeculæ and by the semi-coagulation of the contents which makes the vesicle difficult to empty. Occasionally it is accompanied by fever and, although Massey's original cases, with one exception, recovered within a week or ten days, natives regard the disease with dread, owing to its reputation for deadliness.

The majority of victims are young adults. The onset is sudden and the early symptoms are lassitude, general dullness, and suffusion of the conjunctivæ, with pyrexia, sometimes of 103–104° F. There is tenderness over the parotids and vague pains. These are soon succeeded by widespread hæmorrhages into the skin and mucous membranes. In natives the cutaneous hæmorrhages are most easily seen in the axilla. Stein and Miller remark the constant association of cutaneous *purpura*, which is easily missed on black skins. Bullæ are seen on the lips, buccal mucosa, tongue, and palate, the last-named in particular. Epistaxis occurs in practically every case and subconjunctival hæmorrhages are in evidence. Bleeding occurs from the bowels as well as from the bladder. At autopsy hæmorrhagic vesicles are found in the serous membranes, the pleura, peritoneum and diaphragm. A common finding is hæmorrhagic bronchopneumonia. Usually there are large retroperitoneal perirenal hæmorrhages. Blackie found involvement of the central nervous system in one of his cases. The bleeding time of the blood is increased, and there is a reduction in blood platelets. Normoblasts may be present. The blood sedimentation rate is slightly increased. Blackie thought that onyalai is an acute form of essential thrombocytopenia due to defective nutrition. Stein and Miller (1943), who carried out a fine piece of work, found that onyalai is not confined, as had been thought, to native races. It is quite common in the Transvaal and Northern Bechuanaland. In Africa it extends from the equator to 26° south latitude, Johannesburg being the most southerly point. They studied 21 cases which could be classified as mild, severe or acute. The youngest patient was a native female aged 7 months. Hæmorrhagic bullæ are peculiar to onyalai, and not found in other forms of thrombocytopenic purpura, suggesting some toxic factor. The course of the disease is aggravated by the menses in women, and response to treatment is similar to the acute incipient episodes of idiopathic thrombocytopenic purpura.

The diagnosis has to be made from snake-bite, in which hæmorrhagic symptoms may supervene.

Blackie found that the most effective treatment was by blood transfusions and by injection of 18 c.c. of donor's blood intramuscularly into the buttocks or outer aspects of the thighs, but Stein and Miller found the intravenous route better. They suggest that splenectomy is indicated in patients who relapse after this treatment.

VII. Chiufa ("Chinkumbi" and "Kanyemba")

This is a disease resembling acute gangrenous rectitis described in the earlier editions of this manual, which has been reported from South America. Gilkes described cases he had under his care in Northern Rhodesia. It is found in the Luangwa and Lusenfwa valleys at an altitude of 2,000–2,500 feet. Its onset is sudden and it runs an acute course. The primary manifestation is stated to be a white powdery condition which appears round the anus and gives the appearance of "boracic acid or flour"; in women it covers the vulva as well. After a few days this disappears and the patient becomes acutely ill with pains in back and neck and a temperature of 104° F. The anus becomes relaxed and the rectum can be seen protruding, red and angry. Throbbing in the rectum is noted, and constipation is the rule. The inflammation travels up the large intestine until the colon is involved, when there may be diarrhœa and vomiting. In women the vagina also may be affected.

VIII. Tropical Eosinophilia

A new entity was described by Frimodt-Möller (1940) and Weingarten (1943) in India. This is characterized mainly by spasmodic bronchitis, leucocytosis and high eosinophilia. It affects mostly people who live by the sea, and has apparently no relationship to any other disease but is thought to be a form of allergy. The physical signs are those of bronchial asthma. During the febrile periods the spleen is moderately enlarged. The most striking feature is massive eosinophilia, which accounts for the considerable leucocytosis. It may reach 90 per cent. and is higher than in any other disease, except eosinophilic leukæmia. The X-ray shows disseminated mottlings in the lung, the average single focus being the size of a split pea, somewhat similar to silicosis. The disease is benign and lasts for years, but reacts to intravenous injections of neoarsphenamine in courses of six doses of 1·15 to 0·45 grm.

This description closely resembles that of *Löffler's syndrome*, which is like pulmonary tuberculosis (Freund and Samuelson, 1940). The cause is unknown. Engel in China (1936) and Koino in Japan ascribe it to allergy from privet blossoms, but this has not been observed elsewhere. In some respects it resembles pulmonary coccidioidomycosis (*see* p. 609).

The discovery by Carter and his colleagues (1944) of mites (*Tyroglyphus* and *Carpoglyphus*) in the sputum of these patients is interesting, but awaits confirmation. It is possible that the syndrome may be evoked by sensitization to intestinal parasites, such as *Ascaris* or *Ancylostoma* (*see* p. 765).

Section IX.—ANIMAL PARASITES AND ASSOCIATED DISEASES

CHAPTER XLI

PARASITES OF THE CIRCULATORY SYSTEM : BILHARZIASIS (SCHISTOSOMIASIS)

Definition.—A group of diseases caused by certain digenetic trematodes of the family Bilharziadæ which inhabit the venous system of man in various tropical and subtropical countries.

I. GENITO-URINARY BILHARZIASIS (*Bilharzia hæmatobia*) or *Schistosomiasis*

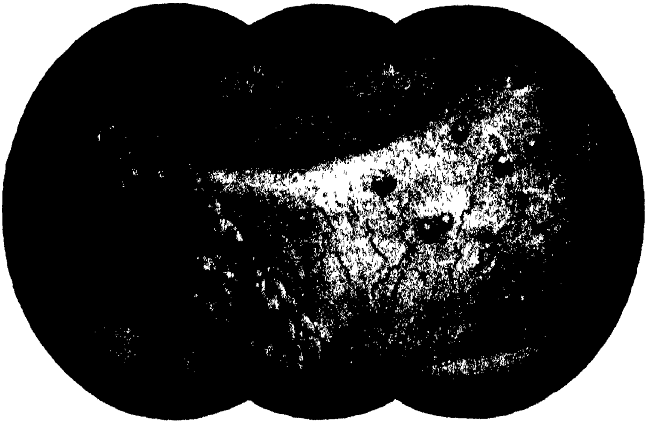
Synonyms. Schistosomiasis; Bilharziasis; Bilharzia Disease; Endemic Hæmaturia.

Definition.—A chronic endemic disease produced by infection of the pelvic veins, particularly those of the bladder, and occasionally those of the rectum, by *Bilharzia hæmatobia*, the eggs of which, being deposited in the mucous membrane, give rise to hæmaturia, cystitis or other symptoms connected with the urinary organs, and occasionally, when deposited in the rectum, to muco-sanguineous discharges from the bowel. The eggs of the parasite are discharged in the urine and, in certain cases, in the fæces.

History.—Hæmaturia has been known to exist in Egypt since the earliest times, and the eggs of this parasite have been found in mummies by Ruffer. Bilharz, in 1851, originally discovered the parasite, which was named *Bilharzia* by Cobbold in honour of its discoverer, but until quite recently it was considered that the generic term *Schistosoma* of Weinland had scientific priority.

Geographical distribution.—The eggs of this parasite were identified by Harley in Natal in 1864, and since then the disease has been found in other parts of Africa, more particularly along the eastern side of the continent, as far south as Port Elizabeth, and it is common throughout the Union of South Africa, especially in Natal. In Central Africa it occurs in the Northern Sudan, Uganda, the Congo, Rhodesia and in North Abyssinia; it is met with in West Africa as well, especially in Liberia and Sierra Leone. In North Africa it is especially common in Morocco, Algeria, Tunis and Egypt. It also occurs in Arabia, parts of Palestine near Jaffa, Persia, Iraq, Cyprus, in the town of Tavira in Portugal, in Mauritius, Réunion, and Madagascar. A few indigenous cases were reported, over forty years ago, from Western Australia. (Map V).

Precise information about the ravages of bilharziasis in Egypt are forthcoming. Scott, as the result of 40,000 examinations, found that in the northern and eastern edge of the Delta, reaching as far as Cairo, 60 per cent. of the inhabitants are infected with *B. hæmatobia*, and an equal number with *B. mansoni*; in the apical southern half of the Delta, however, though still 60 per cent. are infected with *B. hæmatobia*, only one-tenth of that number have *B. mansoni*. The line between the first and second areas is sharp and defined,



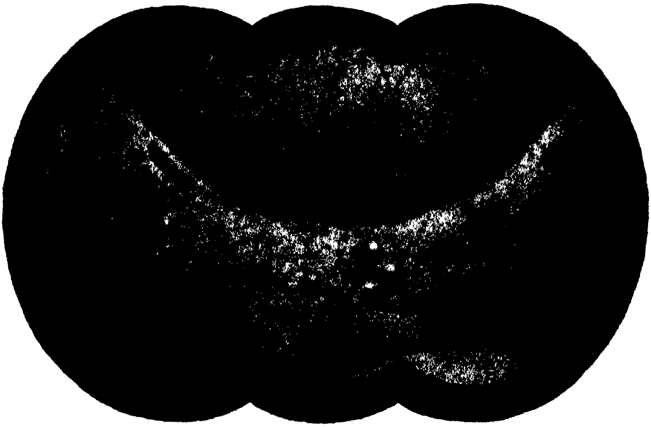


Fig 2

Bilharzial disease of the bladder before treatment, and one month after treatment with sodium antimony tartrate. The yellow nodules in Fig. 1 are the dead ova working their way through into the bladder cavity. They do not indicate active bilharzial disease.

(By permission of Brit. Journ. Surgery and Dr. J. B. Christopherson.)

BILHARZIASIS OF THE BLADDER.

PLATE XX

and does not correspond to any noticeable topographic, hydrographic or demographic variation. Moreover, there appears to be no difference in the number of planorbis snails, the intermediary hosts of *B. mansoni*, in these two regions. In the northern two-thirds of that part of the Nile Valley between Cairo and Assiut, *B. hæmatobia* infects 50 per cent. of the population, but *B. mansoni* and planorbis snail are absent. In the southern third, where old *basin* irrigation—that is irrigation at flood Nile—takes the place of the new perennial irrigation, *B. hæmatobia* alone is present, but infects only 5 per cent. of the population. Heavy infection with *B. hæmatobia* is associated with perennial irrigation from high-level canals, which takes the place of flood irrigation, with alternate flushing and drying. In the district where 5 per cent. of the inhabitants are infected with *B. hæmatobia*, 1 in 1000 die from this infection : in the Northern Delta district, this proportion rises to 1 in 22 (Fig. 248B).

Ætiology. *Parasite.*—*Bilharzia hæmatobia* is a unisexual trematode. The *male* measures 1-1·5 cm. in length by 1 mm. in breadth ; its cylindrical appearance is due to the infolding of the two sides of the body to form a gynæcophoric canal. The *female*, darker, but longer, 2–2·5 cm. in length, is partially enclosed in the gynæcophoric canal of the male. The parasites live in the blood of the portal vein and its mesenteric branches, but numbers dwell also in the pubic, vesical, and uterine plexuses. The longevity of this parasite is phenomenal, as it may remain active and produce viable eggs for more than thirty years.

The *eggs* are oval, and are provided at one end with a definite spine. They measure 0·16 mm. by 0·06 mm. Normally they are voided in the urine, exceptionally in the fæces. It has been pointed out by Khalil that the hatching of the egg in water is due to osmotic pressure ; a 0·75 per cent. salt solution completely inhibits this process.

Life-history.—On coming into contact with water, the eggs hatch and give rise to an active, ciliated embryo or miracidium, which, as a rule, enters a fresh-water snail, usually of the genus *Bulinus* ; in the liver or hermaphrodite gland of this mollusc it develops into sporocysts, eventually into active, bifid-tailed cercariæ which, on escaping from the snail, re-enter man by burrowing through his skin. Some cercariæ pass through the lung capillaries to the heart and are distributed all over the body, including the skin. Many are held up and die, giving rise to a secondary cutaneous reaction with wheals and blotches due to breaking down of cercariæ. Those which get to the mesenteric capillaries of the bowel wall reach the portal system where they grow until almost sexually mature and become paired. They then return against the stream to the mesenteric veins to lay eggs. (For further details regarding the life-history of this parasite, *see* p. 890.)

Pathology.—The changes brought about by the bilharzia vary very much according to the degree and duration of the infection (Plate XX). In almost every case the walls of the urinary bladder are early affected. All that may be apparent to the naked eye at this stage is a certain amount of injection of the small vessels of the mucosa vesicæ, and certain exceedingly minute vesicular or papular elevations of the surface of this membrane. When these minute elevations are examined microscopically they are found to contain eggs even in minute blood-vessels. Later, especially in the trigone of the bladder, there are rounded patches of inflammatory thickening which project somewhat, are granular on the surface, and dense ; on section they creak under the knife as if they contained gritty particles. It is evident that these elevated, thickened patches are the result of an inflammatory process provoked by the clusters of eggs which the microscope reveals scattered throughout their entire extent. The eggs are principally deposited in the submucosa, less extensively in the mucous membrane, still less abundantly in the muscular walls of the organ or in its subserous connective tissue. They tend to occur in groups, each of which is invested with a connective-tissue capsule ; or they may be lying in small blood-vessels which they occlude. Some eggs are seen to have undergone calcification ; others are still fresh, either segmenting, or already containing a miracidium. On the surface of the rounded patches already mentioned, phosphatic deposits, also containing eggs, are not uncommon ; from their yellow glistening appearance they are known as " sandy patches ", and sometimes they present minute sloughs. (Fig. 133.) Besides these indurated patches, various forms of polypoid excrescence—sometimes ulcerated—may protrude from the mucous surface into the cavity of the bladder. These various hyperplasiæ frequently contain the adult parasite as well as eggs. Ferguson and others described a nodular form of bilharziasis, an affection of the subperitoneal surface of the bladder, which closely resembles tuberculosis.

In addition to what may be designated the specific changes in the mucosa, the muscular coats of the bladder are generally hypertrophied. In consequence of this, as well as of the ingrowth of villosities and different forms of new growth, the capacity of the organ may be much diminished. Its mucous surface is generally coated with a sanguineous mucus containing myriads of eggs. Gravel or small stones—generally phosphatic—are sometimes found either embedded in lacunæ in the hypertrophied and roughened bladder-wall, or free in the cavity. Not infrequently a similar hyperplasia occurs in the ureters, and particularly towards their lower ends, even at an early stage. In rare instances the pelvis of the kidney is affected. Obliteration of the ureter, both from small stones and from thickening of the mucous membrane, not infrequently results ; this leads to dilatation of the pelvis and atrophy of the parenchyma of the kidney. It is easy to understand how, in time, these changes in the bladder and ureters may give rise to hydronephrosis, pyelitis, abscess of the kidney, and similar secondary affections. Hyperplasia of the prostate due to infiltration with eggs is sometimes found.

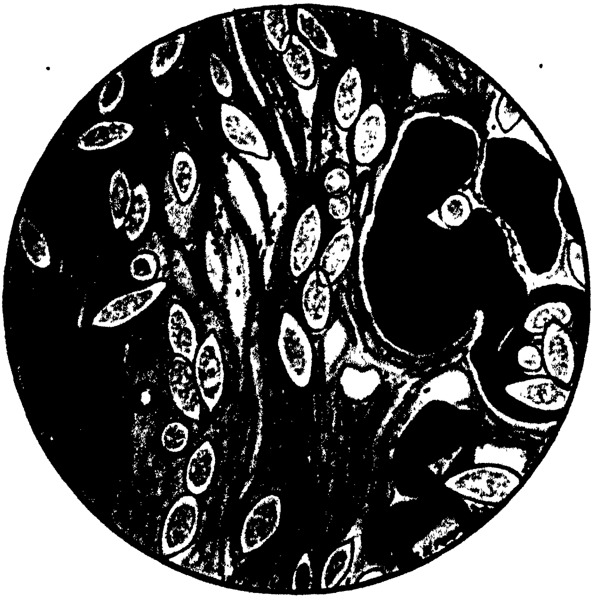


Fig. 132.—Section of bladder-wall, showing eggs of *Bilharzia hæmatobia* in tissues.

Hyperplasia from bilharzial infestation may also occur in the vesiculæ seminales, penis, walls of the vagina, and cervix of the uterus, leading to corresponding bloody, egg-containing discharges.

Bilharzia eggs in small numbers have been found in the liver, in gallstones, in the heart, and in the kidneys, and occasionally in the brain, spinal cord, and lungs. Tumours of bilharzial origin have sometimes been met in connection with the peritoneum and ligaments of the uterus. The egg-production of *B. hæmatobia* is slower than that of *B. mansoni.* They get to the lowest branches of the mesenteric veins, some even to the rectum, when eggs may appear in the fæces, but most migrate through the hæmorrhoidal vein to the venous plexus of the bladder. When the eggs are deposited eosinophil cells are attracted and may produce micro-abscesses, forming pseudotubercles on the peritoneal surface of the bowel with resulting connective tissue. If they occur on mucous surfaces they take the form of small erosions or ulcers. Giant cells form and may completely absorb the egg.

The eggs can be conveniently demonstrated in the tissues by digesting selected portions in 3 per cent. potash solution.

Symptoms.—The symptoms produced by *B. hæmatobia* vary in degree within very wide limits. In the vast majority of cases the patient experiences no trouble whatever; in other instances suffering is very great. Indirectly, from the serious lesions of the urinary organs to which it may give rise, this bilharzia is an occasional cause of death.

Early toxic symptoms, such as pyrexia with urticaria, have been noted, and may come on four weeks after exposure to infection. The *incubation period* of definite disease, on the other hand, varies from three months up to two and a half years. The cercariæ, on penetrating the skin, produce an irritative dermatitis as in other forms of bilharziasis. (*See* p. 693).

The most characteristic symptom of the presence of the parasite in the wall of the bladder is the passage of blood at the end of micturition, with or without a sense of urinary irritation. The quantity of blood passed and the degree of irritation are increased by exercise, by dietetic indiscretions, and by all such causes as are calculated to induce or aggravate cystitis. As a rule, it is only the last few drops of urine that contain blood; sometimes, however, the hæmorrhage is more extensive, and then the entire bulk of the urine may be blood-tinged. Occasionally, clots are passed.

If, in a case of moderate infection, the urine be passed into a glass and held up to the light, minute flocculi or coiled-up mucoid-looking threads will be seen floating about in the fluid. If it be allowed to stand, the flocculi, and perhaps minute blood-clots, will subside to the bottom of the vessel; these, on being taken up with a pipette and placed under the microscope, will be found to contain, besides blood-corpuscles and catarrhal products, large numbers of the characteristic terminal-spined eggs.

In doubtful cases, where eggs are few, the best way to find them is to get the patient to empty the bladder and to catch in a watch-glass the last few drops of urine which can be forced out by straining; these invariably contain eggs. A low power of the microscope suffices, and is best for diagnosis. Davies in South Rhodesia has remarked upon the peculiarities of the "bilharzial facies," which becomes triangular in outline, with sunken cheeks and prominent malar bones. He considers that this appearance forms a good indication of the disease.

Pain is by no means always predominant; when it occurs it is generally a dull sense of oppression in the suprapubic region, deep-seated perineal pain, or scalding on micturition. Frequency of micturition is an early, and urgency a very common symptom. Rectal symptoms, with passage of blood and mucus, may co-exist with the urinary symptoms, and digital examination may detect ulceration above the prostatic lobes. This localized lesion may be due to *B. hæmatobia* alone, though mixed infections of *B. hæmatobia* and *B. mansoni* are very common, especially in the Nile Valley. Sometimes adult worms *in copula* are passed in the urine; this generally occurs after a copious hæmorrhage from a ruptured vessel.

Endemic hæmaturia lasts for months or years. Spontaneous recovery is rarely complete. In ordinary cases, provided no re-infection takes place, the hæmaturia tends to decrease, although eggs may continue for years to be found in the last few drops of urine passed. In severe cases, sooner or later, signs of cystitis supervene and give rise to a great deal of suffering. Not infrequently the eggs become the nuclei for stone, and symptoms of urinary calculus are superadded. (Fig. 183). Sometimes the pathological changes induced by the parasite in the bladder lead to new growth, in which event the symptoms become more urgent and the hæmaturia excessive. Hypertrophy, contraction, and even dilatation of the bladder are not unusual. Besides the bladder symptoms there may be signs of prostatic disease, or of disease of the vesiculæ seminales, causing spermatorrhœa. In the latter case, eggs may be detected in the semen. In other instances the ureters and kidneys become involved, resulting in ureteric dilatation and hydronephrosis. Secondary infection of the urinary tract with septic cystitis commonly supervenes. From the suffering attending these aggravated forms of infection, the patients become anæmic, wasted, debilitated, and a ready prey to intercurrent disease.

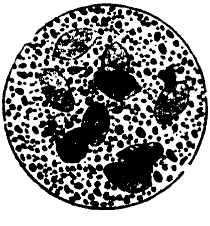


Fig. 183.—Section through nucleus of urinary calculus containing eggs of *B. hæmatobia*.

Milton pointed out the extreme frequency of urinary fistula in Egypt, the result of bilharzial disease of the urethra. These fistulæ may occur anywhere in the neighbourhood of the genitals, but are especially common in the perineum and posterior surface of the scrotum, and originate from infiltration by eggs of the pubic tissue or roof of the urethra just in front of the bulb, the eggs of the parasite being deposited in the mucous or submucous tissue. Stricture of the urethra is by no means uncommon, especially when fistulæ are connected with the floor of the urethra. In the male, infiltration of the penile sheath may result in an elephantoid condition with chordee and actual obstruction to the urinary flow. (Fig. 184).

Makar showed that bilharziasis of the cord and epididymis is by no means uncommon, and is determined by the anatomical peculiarities of the anastomoses between the mesenteric and internal spermatic veins, and, it may be, between the pelvic venous plexuses and deferential veins. The tunica and testes are rarely affected. The onset is very gradual, and it occurs in young adults, whose attention is drawn to the swelling. The cord may be nodular and covered with lentil-like bodies, or it may be enveloped in a single big mass ; the term " bilharzial rosary " well describes the condition. Cytoscopy, sigmoidoscopy, X-rays and complement-fixation tests may be needed for diagnosis, or to differentiate the lesions from somewhat similar swellings due to filariasis, tuberculosis and syphilis. In massive infiltration, the testes may have to be removed ; in the early stages medical treatment is effective.

The majority of infections of bilharzial disease of the spermatic cord are due to *B. hæmatobia.* The following figures are given by Makar : infection with *B. hæmatobia*, 88 per cent. ; with *B. mansoni*, 27 per cent. ; mixed infection with *B. mansoni* and *B. hæmatobia*, 35 per cent.

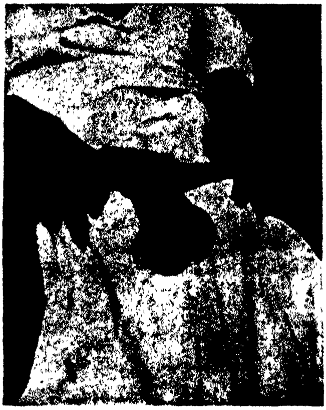


Fig. 134.—Urinary bilharziasis : pseudo-elephantiasis of penis, due to infiltration by ova. (*After Madden.*)

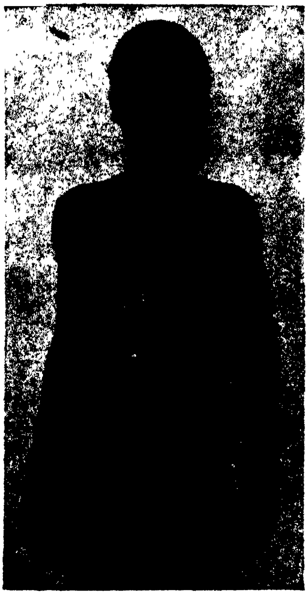


Fig. 135.—Bilharziasis of the Congo with splenomegaly. (*Dr. C. C. Chesterman.*)

Makar has reported one case of primary bilharzial disease of the gall-bladder, giving rise to duodenal stasis. The interior of this viscus was studded with sandy patches like those seen in the urinary bladder.

Vaginitis and cervicitis are also produced by this parasite. Papillary growths and ulcers may be mistaken for carcinoma. On the vulva, papillomatous masses containing bilharzial eggs are, according to Madden, common. Similar excrescences about the anus, in the groin and perineum can be distinguished from venereal warts by microscopical examination.

Large numbers of eggs, as pointed out by Turner, may be deposited in the lungs, where they give rise to a form of interstitial pneumonia. According to Day, Shaw and Ghareeb, signs and symptoms of Ayerza's disease may be simulated. Mainger stated that in *B. hæmatobia*, as well as in *B. mansoni* infections, latent pulmonary involvement is usually present, even in the absence of pulmonary symptoms, and that by use of X-ray films the lesions can be verified about three months after infection. Eggs have been found also in the brain and spinal cord, thus accounting for epileptic and paralytic symptoms from which the patients had suffered, but these supervene only in hyperinfected individuals. One case of bilharzial myelitis was described by Day and Kenawy, with the customary symptoms. At autopsy eggs of *B. hæmatobia* were demonstrated in the lumbar enlargement of the cord.

Chesterman found certain districts in the Congo where eggs which appeared at first to be *B. hæmatobia* are found only in the fæces, giving rise to dysenteric symptoms closely resembling those produced by *B. mansoni*, but in this instance they are longer and with more attenuated extremities than those usually seen in the urine (*see* Appendix, p. 892). Similar conditions have been recorded from the Assiut district of Egypt, where only *B. hæmatobia* is present.

Fisher, at the instigation of Chesterman, brought forward a considerable amount of evidence that this Congo bilharziasis is not due to *B. hæmatobia* as was thought, but to *B. intercalata*, a species which in its morphology is intermediate between that of *B. hæmatobia* and *B. bovis*. The spindle-shaped eggs resemble those of the latter species and also of *B. mattheei*, with terminal well-developed spine, which may attain a length of 20 μ. The intermediary host appears to be *Physopsis africana*. Zellweger found this species commonly in Gaboon, along the course of the Ogowé river and its tributaries.

The *symptoms* produced by *B. intercalata* appear to be mild; in Yakusu (Congo) it has been found that 50 per cent. of the school-children are infected; their health is not seriously affected, but sometimes spleen and liver are enlarged. Dysenteric symptoms and abdominal pain constitute the only outward signs of the disease, and pulmonary manifestations (in contrast to *B. hæmatobia*) are practically absent. Toxic manifestations, which usually accompany massive infections with *B. mansoni*, or *B. japonica*, have been noted. (Fig. 135.) The hepatic and intestinal symptoms run a similar course, with urticaria and bronchial asthma. The infected bowel, as seen by sigmoidoscopic examination, has a granular appearance suggesting sandpaper, and there are petechiæ of minute size, but no polypi or ulcers.

Bilharzial appendicitis, due to accumulation of *B. hæmatobia* eggs in the appendix, is a clinical entity. Lovett Campbell, in northern Nigeria, found them in 57 per cent. of all appendices removed at operation, and considers that this infection may produce symptoms requiring urgent surgical intervention. Barsoum, on the other hand, stated that it does not cause or predispose to appendicitis of the inflammatory type.

Diagnosis.—The diagnosis of this disease is not difficult; the presence of eggs in the urine is decisive. (Figs. 186, 187.) In countries like Egypt, where the disease must often concur with chyluria, with stone, with vesical tumour, with gonorrhœal cystitis, and with pyelitis, as well as with prostatic disease, care must be exercised in each particular case to separate the special factors to which the various symptoms are attributable. Thus, in chyluria with bilharzial disease there will be chyle in the urine in addition to blood. In such a combination the clot which forms will be larger, will contain oil granules and globules, and very probably microfilariæ, in addition to bilharzia eggs; moreover, the microfilariæ will generally be detectable in the finger blood if looked for at night. Stone in the bladder, when suspected, has to be sought with the sound. In gonorrhœal cystitis a history of gonorrhœa will be forthcoming. In prostatic disease enlargement of the prostate may be made out. Difficulty may sometimes arise when eggs are scanty, or have ceased altogether to come away in consequence of the death of the parent worms. The mischief wrought by the parasite remains, although the eggs—the most certain evidence of the parasite's previous presence—may no longer be discharged. But, even if the eggs are very few, they may still be found in the last drop or two of urine passed. If they are not found in the urine, sometimes, by scratching the surface of the bladder with a sound and examining the shreds of mucus so obtained, a few, calcified it may be, but presenting the characteristic spine, may be seen with the microscope. Confirmatory evidence may be obtained from the pus cells, the majority of which are eosinophils. Further evidence may be obtained by the tests described below.

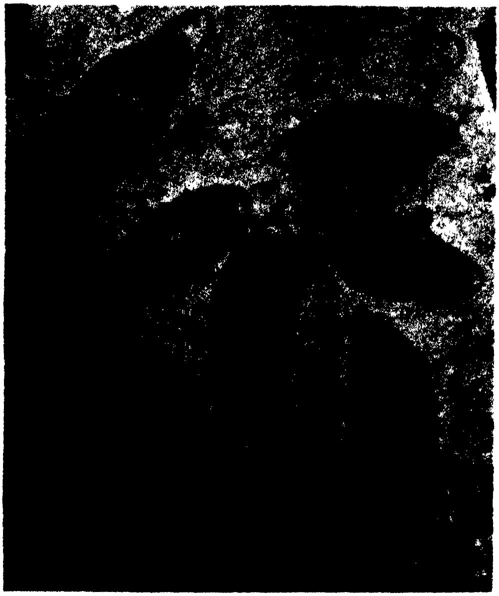


Fig. 136.—*Bilharzia hæmatobia* **eggs in urine, showing contained miracidia.** (*Dr. H. K. Giffen.*)

Complement-fixation.—Fairley in 1917 described a complement-deviation test employing as antigen an extract of the livers of infected snails (*Planorbis boissyi*). This antigen is prepared by macerating a number of livers containing cercariæ of *B. mansoni* in absolute alcohol, filtering, and evaporating by means of a Sprengel's pump. A saline extract is then made of the dried residue and its anti-complementary dose estimated. The general technique is the same as for the quantitative Wassermann reaction in syphilis.

The reaction is apparently a group reaction, in so far as an antigen prepared from cercariæ of *B. mansoni* will give positive results with *B. hæmatobia* serum in 89 per cent. of early cases; further, Bettencourt and Borges stated that similar reactions take place with *Fasciola hepatica* antigen. A positive result may be obtained in early infections even before the appearance of eggs in the dejecta. It is not so specific in the later as in the earlier stages, but may be employed as a check to treatment.

Intradermal reaction.—Fairley elaborated an intradermal test, similar to the Casoni reaction in hydatid. A saline extract of dried livers, 0·5 per cent., of *Planorbis exustus* infected with *B. spindalis* of the goat, is used. The extract, having been rendered bacteria-free by passage through a filter, is injected intradermally in a dose of 4 min. A positive reaction is given by an immediate wheal and a zone of erythema with outrunners, and a delayed type of reaction in from five to eighteen hours. This test is useful as a means of diagnosis in all forms of bilharziasis, but remains positive for years after the patient has been cured.

Cystoscopic examination.—In the early stages of the localized disease (within two months of infection) the cystoscope reveals sparse grey discrete elevations in the trigone around the ureteric orifices; later, definite hæmorrhagic papules appear with surrounding inflammation. Later still, characteristic "sandy patches," resembling ridges of sea-sand, with papillomata, can be distinguished. (Plate XX). These appearances are pathognomonic.

Prognosis.—An important element to be considered in venturing on a prognosis is the long life of the parasite. Another important element in prognosis is the degree of infection: the greater the number of parasites, the more severe and the more extensive is the disease they produce. As with filarial infection, the greater the number of cases in a district, the greater the proportionate probability of severe infections. The prognosis is practically that of a chronic cystitis depending on a remediable, and not in itself fatal, cause. Much suffering may often be produced, and, as a consequence, anæmia and debility. Possibly calculus may be formed; possibly grave renal disease may ensue; possibly, eventually, villous or epitheliomatous growths in the bladder. In the milder degrees of infection which fortunately are the commonest, the patient seems to be in no way inconvenienced by the parasite, and generally escapes all serious consequences. In any case, mild or severe, there may be attacks of hæmaturia from time to time; as a rule, the quantity of blood thereby lost is insignificant.

TREATMENT

Preliminary statement. The successful treatment of bilharziasis by intravenous injection of sodium-antimony tartrate is due to Christopherson. His results have been abundantly confirmed. The drug appears to act upon the adult trematode by cumulative action, and results are judged by observation upon the eggs in the urine. According to Dye, the adult stage of the parasite is most readily affected by tartar emetic; cercariæ and miracidia are less susceptible, while eggs are not affected to anything like the same degree. To test the effect of this drug the freshly-passed urinary deposit is mingled with about sixty times as much warm water at 130° F., and the hatching of the eggs is observed. Under normal conditions this takes place in about five minutes, but after several injections of antimony tartrate they become dark and shrivelled and contain dead miracidia. Christopherson believes this change to be due to the direct action of antimony upon the eggs (Fig. 138). *Fairley*, from experimental studies on the allied *B. spindalis* of the goat, believes that antimony acts selectively on the reproductive organs of the female bilharzia, and thus brings about firstly, the shrunken appearance of the egg and, secondly, cessation of egg-laying capacity.

It should be noted that living eggs left in too long contact with alkaline urine fail to hatch; therefore all experiments should be performed with freshly-voided urine.

Potassium antimonyl tartrate may also be used (*see* p. 824).

I. Tartar emetic (Sodium antimonyl tartrate).—Intravenous injections are given on alternate days over a period of four to six weeks. It is customary to begin with ½ gr. of tartar emetic dissolved in 10 c.c. of freshly-distilled sterile water, and gradually to increase the amount by ½ gr. until the maximum individual dose of 2–2½ gr. is reached. It is not always necessary to dilute the antimony with 10 c.c. of water; for amounts under 1 gr., 6 c.c. suffices. Some toxic phenomena may be avoided by dissolving in 5 per cent. glucose solution. Antimony tartrate solution should not be boiled for any length of time nor subjected to pressure. For large numbers of patients stock solution of tartar emetic is made up in a sterilized vaccine bottle with a rubber cap in a strength of ½ gr. to 1 c.c. of distilled water; this can be further diluted later. The solution should be drawn into a syringe of 10 c.c. capacity, and slowly injected into the median basilic or cephalic vein. The total amount injected to kill all adult trematodes is about 25–30 gr. of tartar emetic. Rapid improvement in the condition of the urine is soon observed; generally all traces of blood disappear after the injection of 15 gr. For children a total of 10 gr. appears to be sufficient, the maximum individual dose being 1 gr. This course of treatment, once commenced, should be persisted in; cases almost invariably relapse if there are interruptions for a week or longer. In Egypt (1925) the course consisted of twelve injections three times weekly till 22½ gr. of the drug had been administered, and occupied four weeks. When a small amount of diluting fluid is utilized, as suggested, evidences of toxic absorption are noted, such as headache, cough, nausea and transient rheumatic-like pains, especially in shoulder joints.

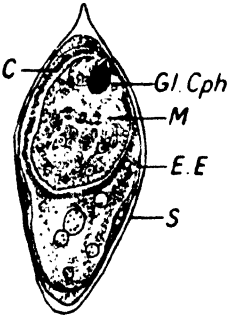


Fig. 137.—Egg of *B. hæmatobia* to show de-development of miracidium.

S, shell; *E.E.* embryonic envelope; *M*, miracidium; *C*, cilia; *Gl. Cph.* cephalic glands.

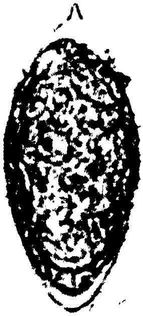


Fig. 138.—Egg of *Bilharzia hæmatobia*, showing changes produced in contained miracidium by antimony tartrate. (*Dr. John Anderson.*)

Fairley confirmed the specific action of tartar emetic on the adult worms. In *B. spindalis* infections of the goat, he showed that tartar emetic, in doses of 3·9 to 5·5 mg. per kilo, at daily intervals for a period of from sixteen to twenty-six days, kills the adult parasites and eradicates the disease. Pentavalent compounds of antimony (Neostibosan, Neostam, etc.) do not seem to be so efficacious as tartar emetic.

II. **Anthiomaline** (*Lithium antimony thiomalate*) is recommended by Moulinard as a more efficacious drug than emetine or tartar emetic. There are no contra-indications ; intramuscular injections are not painful, and there is no evidence of either local or general reactions. Anthiomaline is very soluble and contains 16 per cent. of antimony. It is supplied in 2 c.c. ampoules of a.6 per cent. solution containing 0·02 grm. of antimony. The initial dose is 0·5 c.c. for a child of twelve and 1·5 c.c. for others. The maximum individual dose for an adult is 4 c.c., for a child of twelve 2 c.c. ; and the total dosage is about 65 c.c. It is best given by the intravenous route on alternate days.

III. Stibophen.—This 6·3 per cent. aqueous solution of sodium antimony *bis.* —catechol—3 : 5—disulphonate has largely replaced tartar emetic for intramuscular and intravenous injection. It contains 8·5 mgm. of trivalent antimony per c.c. For adults the initial dose is 1·5 c.c. and 3·5 c.c. on the second day, 5 c.c. being the maximum dose. Thereafter, injections are made on alternate days. Total dosage varies from 40 to 75 c.c. For children the initial dose is 0·5 c.c. and the maximum 3·5 c.c. ; the maximum total dosage is 47·5 c.c. A full course of treatment averages 29 days. Stibophen is non-irritating, causing few local reactions, and is almost identical with Fouadin.

IV. Fouadin (Neoantimosan).—A trivalent compound—antimony pyrocatechin disulphonate of sodium (containing 13 per cent. of antimony) —was introduced in 1929, for the treatment of bilharziasis in Egypt. It is claimed that a cure may be effected in nineteen days, in contradistinction to the more prolonged tartar-emetic treatment. The drug is given *intramuscularly* in 7 per cent. solution, and is put up in ampoules. The dosage is as follows :

For an adult :	1st day	1·5 c.c.
	2nd ,, ...	3·5 ,,
	3rd ,, ...	5 ,,

Subsequently 5 c.c. on alternate days up to the 15th.

The total number of injections should be from ten to fifteen, totalling 0·4 grm. of antimony. Of this quantity 50 per cent. is excreted in the urine and 4 per cent. in the fæces. Late vomiting occurs in 2·5 per cent. of the cases. There is apparently no local reaction except, occasionally, spasms of coughing. The urine is examined after the last injection, and if living eggs are still present further injections are indicated. According to Khalil (1930), in 1,474 cases treated with fouadin a cure was obtained in 97·6 per cent. It is generally considered that the results are by no means so satisfactory as by the older method with intravenous tartar emetic.

Orenstein stated that fouadin should never be given *intravenously*, but should be administered intramuscularly on alternate days. In over 300 school-children treated in this manner no toxic symptoms were observed. The toxic effects of antimony therapy are given on p. 166. Overdosage must be avoided. One of the most serious and permanent injuries is retrobulbar neuritis with central scotoma and loss of colour sense.

V. Emetine.—There is some evidence that emetine also is toxic to bilharzia (Diamantis and Erian). The injections should be given intramuscularly to children who are intolerant of antimony, or whose veins are too fine for intravenous injections; generally treatment is commenced with ½-gr. doses, the maximum single dose for a child being 1 gr., while an aggregate total of 15–20 gr. is recommended. Tsykalas, who reported results in 3,800 cases, injected the drug intravenously in doses of 1½ gr. daily, the total course lasting 10–14 days, and 15–17 gr. (1·12 grm.) being injected. Toxic symptoms—diarrhœa, vomiting and neuritis—are apt to ensue. In his later communications Tsykalas claimed that emetine is superior to any other. The biggest doses should be given at the commencement of the course and should be given daily. The heart's action must be carefully watched, and the size of the dose regulated by body-weight. Two months should be permitted to elapse between individual courses of treatment.

TABLE X.—DOSAGE OF ANTIMONY COMPOUNDS

Compound.	Percentage of Antimony.	Total Dosage.
Ant. potass. tart.	36	1·9 grm.
Ant. sodii. tart.	39·5	1·6 grm.
Stibophen.	13·5	40-75 c.c.
Fouadin.	13·5	60-65 c.c.
Anthiomaline.	16	50-65 c.c.

Local measures.—Stone and troublesome new growths are removed by operation. Mackie and others reported good results from perineal cystotomy and drainage when distress is extreme. Perineal fistula must be dealt with on ordinary surgical principles. Hyperplasia of the vagina and cervix is best treated by scraping. If, by care, re-infection from water can be avoided, there is no need to send the patient away.

Prophylaxis.—In the endemic districts, children, in particular, should be carefully and repeatedly warned, by school and religious teachers, against drinking or bathing in rivers, ponds, and canals. (Fig. 139.) Sportsmen should be warned against wading, especially when shooting snipe, in localities known to be infected; even fishing in fresh-water canals in countries like Egypt is not free from risk. Swamps, when slightly brackish, are safe. Drinking-water should be boiled, and every care must be exercised to prevent the diffusion of the disease by prohibiting the evacuation of excreta into or near water, where the miracidia might find the opportunity of development and transmission. This prohibition should not be restricted to patients exhibiting definite symptoms of the disease, but extended to all, because, as special inquiries have shown, a large proportion of the infected do not suffer from any troublesome symptom and are often unaware of their infection. Leiper pointed out that much might be accomplished by attacking the mollusc intermediary and the free cercariæ. For the former, he suggested periodic drying of irrigation canals and the use of chemical manures; and for the latter, the use of cercariacides such as sulphate-of-soda tablets for drinking-water, boiling, and lysol, creolin, or cresol (1 in 10,000) for bathing-water. Chlorine, in the strength (1 in 1,000,000) generally used in tropical countries to sterilize water, appears to have no lethal effect upon living cercariæ.

Witenberg and Yofe showed that chlorine is the only agent which can be depended upon to kill cercariæ, and that chloramine is the most effective form. Chlorine water, containing 2 grm. per litre, is prepared by introducing gaseous chlorine directly into the water; 2 grm. of ammonium chloride (NH_4Cl) is then dissolved in 100 c.c. of this chlorine water, and the solution is left to stand for two hours at room temperature. Of this 2·5 c.c. are dissolved in one litre of water. This forms the stock solution, which contains from 1–2 per million of active chloramine. For military purposes in the field, Sprowle recommended half hour contact with water-sterilizing powder containing 23·85 per cent. chlorine

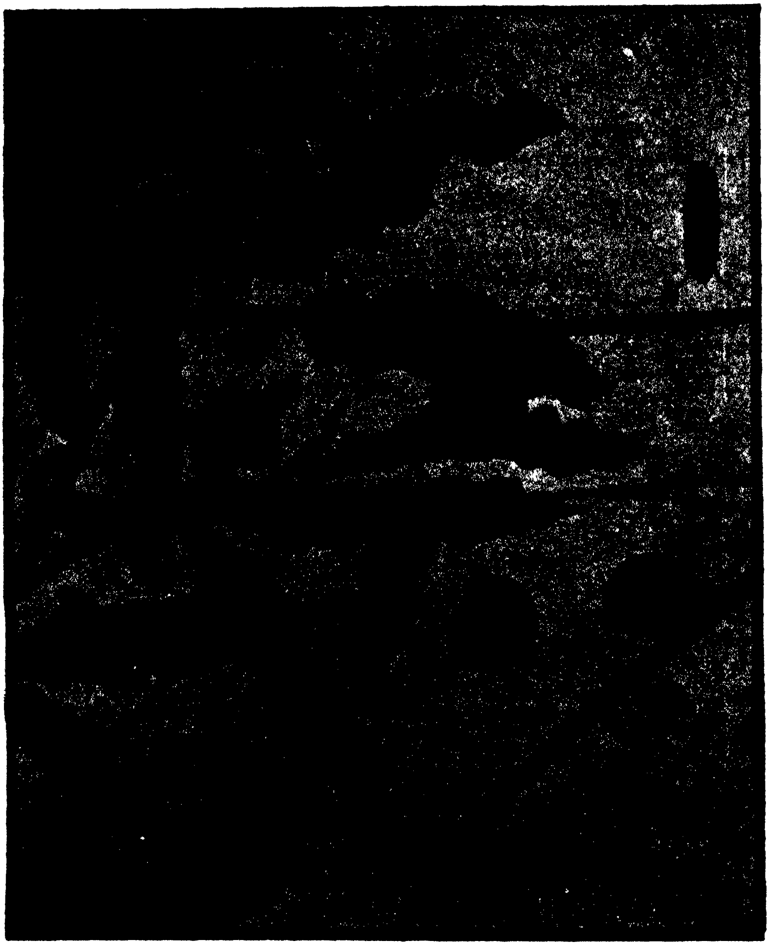


Fig. 139.—The intermediary hosts of *B. hæmatobia* **and** *B. mansoni* (*Planorbis boissyi* **and** *Bullinus contortus*) **in their natural surroundings.** Nat. size. (*J. K. Lund, del.*)

at a temperature between 27·5° C. and 60° C., the dose indicated by Horrocks test, plus one, proving lethal to bilharzia cercariæ.

Ammonium sulphate, under experimental conditions in weak solution, kills snails in a few hours. The free cercaria lives but a short time—at most forty-eight hours—in water, but a mollusc once infected continues so for months. The free cercariæ readily pass through the ordinary municipal filter-bed, for they can traverse 30 in. of fine sand in five hours ; but they perish if they do not get access to an appropriate host within forty-eight hours. These facts should be taken into account by the sanitarian.

Alternate drying and using canals for a week or 10 days at a time is not to be depended upon for killing snails—which can withstand desiccation for considerable periods.

The difficulty about the efficient prophylaxis of this and other forms of bilharziasis lies in the habits of the snails, which reappear in pools and water-courses directly the rains re-commence and after they have, to all appearances, been exterminated. Thus in Egypt Khalil states that in 1928 all bulinus snails were completely exterminated in the isolated irrigation region of Wardan in the west of the Nile Delta, by mixing copper sulphate, 1 in 200,000, in the entering water. A few months later they were present in large numbers, some being found on weeds caught by the pillars on a wooden bridge at the entrance of the canal. It therefore seems as if all the canals in the Delta were restocked from the Nile. That infected snails are found in the Nile there appears to be little doubt, for 25 per cent. of the children who have never left Roda Island (which lies opposite Cairo) are infected with *B. hæmatobia*. In 1919 the Editor summed up the situation in Egypt as follows :

> " During the spring months of the year the sluice gates are open and the Nile water is coursing through the canals of Lower Egypt, bearing with it large masses of fresh-water weed and other vegetation, to which infected snails are to be found clinging."

An organized attempt has been made in Egypt, by educational means in schools, by pamphlets, and by diagrams,to deal with the problem effectively. The efforts of the sanitary authorities have received the backing of the religious authorities, but the difficulties are very great and progress must necessarily be slow. These remarks are applicable to *B. mansoni* as well as to *B. hæmatobia* infections. Under the direction of the Under-Secretary of State for Public Health in Egypt, there are fifty-six units engaged in anti-bilharzia work, prophylaxis being mostly upon the therapeutic basis by mass treatment of all infected individuals.

Keeping ducks, which feed on freshwater snails, is recommended.

A novel suggestion for practical prophylaxis of bilharziasis was advanced by Archibald in the use of the fruit of *Balanites ægyptiaca*, a tree which grows naturally in the irrigated areas of Africa, Arabia, Egypt and Palestine. Prophylactic measures suitable for one area are unsuitable for another, and the Arabs resent chemical treatment of their only potable water. *Balanites ægyptiaca* fruits prolifically for six months annually ; the date-like fruit is eaten, but the berries, kernels, bark, roots and branches contain an active principle which is deadly to molluscs, miracidia, cercariæ, tadpoles, and fish. For actual use the berry is advised : one weighing 5·2 grm. suffices to kill bilharzial molluscs

when soaked in 30 litres of water. Thirty-five berries are added to a 4½-gallon petrol-tin of water and stood overnight. The next morning the softened pulp is crushed in water and stood for twenty-four hours, and this suspension is added to a cubic metre of water. This suspension may be obtained naturally if there is a dense afforestation of these trees on the borders of canals and pools which harbour bilharzia-carrying snails.

II. INTESTINAL BILHARZIASIS (*Bilharzia mansoni*)

Synonym. Intestinal schizostomiasis ; Schistosomiasis dysentery.

Definition.—A chronic endemic disease caused by *Bilharzia mansoni*, giving rise to dysenteric and other symptoms referable to the intestinal canal, characterized by appearance of lateral-spined eggs in the fæces. In the early stages there may be general symptoms, such as fever and urticaria, indicating absorption of the toxins excreted by the parasites. One of the visceral manifestations of this infection is Egyptian splenomegaly, a common disease in Egypt and Northern Nyasaland, in many respects resembling kala-azar.

History and geographical distribution.—The occurrence of a bilharzia producing lateral-spined eggs was noticed by Bilharz in 1851, but he confounded it with *B. hæmatobia* ; subsequently several observers encountered female worms with lateral-spined eggs in utero, and the idea of a distinct species suggested itself to Sonsino and others ; but this was discarded for other hypotheses—for instance, that the peculiar position of the spine was due to distortion of the egg-shell in passing through the muscular coat of the rectum.

Manson, in 1903, found numerous lateral-spined eggs in the fæces of a patient from Antigua who had never suffered from hæmaturia. The peculiarities of the case led him to surmise that the lateral-spined egg indicated a new species of bilharzia. In 1907 Sambon, on comparing specimens of the type characterized by lateral-spined egg with *B. hæmatobia* and other species of bilharzia, and taking into consideration its peculiar geographical distribution and distinct pathogeny, proposed that it should be considered a distinct species—*Bilharzia mansoni*. He subsequently described many cases of lateral-spined bilharziasis from South America. Holcomb and da Silva first defined the peculiar anatomical distinctions of *B. mansoni*, but the duality of species was finally settled by Leiper in 1916. He proved that the miracidia, hatching from lateral-spined eggs, after developing in snails of the genus *Planorbis*, developed into adults with constant morphological distinctions. Subsequently this was confirmed by Fairley and the Editor in Egypt, and by Lutz in Brazil.

Possibly this bilharzia is originally a West African species, imported into the New World by African negroes. Its geographical distribution, as far as is known at the present day, extends from the Nile Valley throughout Central and West Africa, the West Indies, and South America ; its range of distribution is limited by that of its appropriate intermediary host. (Map V.)

Epidemiology and endemiology.—*Bilharzia mansoni* requires slightly different conditions for its propagation from those of *B. hæmatobia*, so that, though frequently found associated in Africa, yet there are areas in the Southern Sudan and in West Africa where *B. mansoni* is prevalent and *B. hæmatobia* absent. Although bilharziasis occurs in eleven out of fourteen provinces in the Sudan, *B. hæmatobia* is the common type in the north, and south of the Upper Nile Province *B. mansoni* alone is found. (Map V.)

Infection is acquired during the months of the year when water is sufficiently shallow to permit a high concentration of cercariæ. In inland lakes the seasonal incidence is from October to the end of January, but in the Nile backwaters the danger period is usually February to June.

In South America, especially in Surinam and Venezuela, *B. mansoni* is widespread ; in the latter country it forms an important problem, and 30,000 are infected in one area, the central part of the Northern coastal range where the intermediary, *Australorbis glabratus*,[1] is found. Infestation is commonest where sugar cane is irrigated. In several communities at least one quarter are infected, especially men. Whenever snails occur near houses the women are as highly infected as men, and the children acquire infestation early. The West African green monkey (*Cercopithecus sabœus*) constitutes a reservoir of *B. mansoni* infection in W. Africa, and in St. Kitts in the Lesser Antilles where it now lives in a feral state.

Ætiology.—The parasite much resembles *B. hæmatobia*. The distinguishing features are that it is generally smaller and more grossly tuberculated. There are other points (Fig. 140). The female deposits one or two eggs at a time—a circumstance perhaps explicable by the peculiar structure of the uterus. The eggs are somewhat spindle-shaped, provided with a lateral spine (Plate XXVI, 12, facing p. 1003) and are generally slightly shorter than those of *B. hæmatobia*, 0·15 mm. in length by 0·06 mm. in diameter. These eggs are passed out in the fæces, rarely in the urine, and hatch out a ciliated miracidium. (*See also* p. 893.)

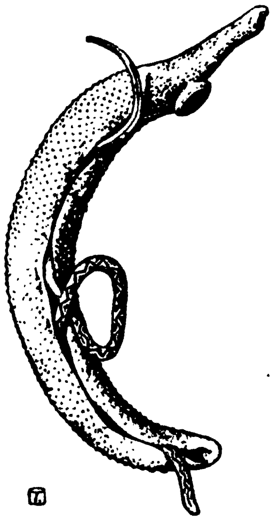


Fig. 140.—*Bilharzia mansoni*, **male and female** × 6. (*After Looss.*)

Pathology of intestinal bilharziasis.—The eggs of *B. mansoni* may be found in great numbers in the liver, where they give rise to a peculiar form of " pipe-stem " cirrhosis. Sandy patches, due to effete calcified eggs, cover large areas of the intestinal surface, and may give rise to acute choleraic diarrhœa. Black pigment granules are deposited in the interstitial and secreting cells of the liver, and have been shown in both *B. mansoni* and *B. hæmatobia* infections, but are commoner and more abundant in the former. It is golden brown or sepia, and gives the same reactions as malarial pigment (hæmatin). The gall bladder has very rarely been found infected. The lymph-glands in the retro-peritoneal tissue are enlarged. There is generally an appreciable hypertrophy of the spleen, which may possibly be attributed to toxic absorption and which gives rise to the clinical syndrome known as Egyptian splenomegaly.

The affections of the colon may be classified into four types—(*a*) those with simple thickening of the mucous membrane ; (*b*) thickening of the mucosa with papillomata and ulcers ; (*c*) pericolic tumours associated with papillomata ; (*d*) polypi of the cæcum which may lead to intussusception. Infiltration of the appendix with *B. mansoni* eggs is not uncommon and may produce the signs and symptoms of acute appendicitis, which is determined by secondary bacterial infection.

---

[1] Formerly

The small intestine is hardly ever affected, except in its lower part. In the colon the disease causes the formation of septic foci, and ulceration of the bowel-wall appears to be produced by the tearing-off of pedunculated papillomata by the peristaltic action of the intestine. By this means, and by sloughing at the base, are produced clear-cut ulcers which may become subsequently infected with *Entamœba histolytica*. Perforation of the bowel may occur. Fairley and Lampe drew attention to the similarity of the disseminated pericolic nodules to miliary tuberculosis and also to infiltration of the mesenteric glands by bilharzia eggs.

Shaw and Ghareeb emphasized the importance of pulmonary damage as the cause of death in *B. mansoni* as well as in *B. hæmatobia* infections. The main damage is due to embolism by eggs derived from female flukes outside the lung They are filtered out in the arterioles which accompany the bronchioles, producing diffuse arterial changes or Ayerza's disease. Parenchymatous tubercles are found containing the characteristic eggs. In some 10 per cent. of cases, the adult worms have been found in the pulmonary veins.

VISCERAL BILHARZIASIS ; HEPATO-LIENAL FIBROSIS ; EGYPTIAN SPLENOMEGALY

Splenomegaly, associated with cirrhosis of the liver, is common in all parts of Upper and Lower Egypt, where 20 per cent. of infants under four years of age are found to have splenic enlargement and anæmia. It is common among the working class at all ages up to thirty ; in the young it is apt to run a severe course, while at a later age the chronic form, progressing to ascites, is met. In children the disease is generally associated with rickets, in adults with ancylostomiasis. A similar syndrome was recorded by Dye from Northern Nyasaland in patients also infected with *Bilharzia mansoni*. Originally, Day came to the conclusion that in Egypt this disease is a peculiar manifestation of *B. mansoni* infection. He regarded it as distinct from Banti's disease in that the hepatic changes are noted from the commencement, while the eosinophilia and recurrent fever disappear under specific treatment with tartar emetic. Hyperplasia of the spleen appears to be secondary to the hepatic cirrhosis, and to this condition are to be ascribed the anæmia and leucopenia which are found in advanced cases. Those with advanced cirrhosis are just those who have few intestinal symptoms, and who pass scanty, or, it may be, no eggs in the stools. Eggs of *B. mansoni* may be found on digestion of solid organs, such as the liver and spleen, with potash.

Pathology of hepato-lienal form.—Ferguson recorded that the average weight of the spleen is 30 oz. ; it may reach 300 oz., and, according to Day, may contain scanty eggs of *B. mansoni*. It is firm ; microscopically there is a general hyperplasia with active phagocytosis of red cells by macrophages.

Onsy stated that the only certain method of finding eggs in these spleens is by macerating the tissues in 20 per cent. soda solution and then centrifugalizing. The eggs are phagocytosed by giant cells, a process accompanied by considerable eosinophilia. In order to account for the widespread nature of the visceral lesions and the paucity of eggs, the view was put forward by Girges and others that Egyptian splenomegaly is caused by infection by male *Bilharzia mansoni*, in the absence of the female ; but this view is not widely held. On the other hand the presence of " spinster " females has been reported.

Abdel Shafi claimed that, although the incidence of eggs in the liver is fairly high, yet other organs and tissues show much heavier deposits, that infection of the liver alone is unknown, and that the number of eggs in the liver substance is small in comparison with the extensive cirrhotic changes in that organ.

The liver is usually enlarged in the early stages, and presents the picture of early multflobular cirrhosis with isolated necrotic foci. In the more advanced stages the organ is shrunken and firmly fixed to the diaphragm by adhesions. There is a comparative absence of bile-duct formation. The bone-marrow shows no great disturbance of the hæmopoïetic system.

Symptoms of intestinal bilharziasis.—As in *B. hœmatobia* infections, the earliest manifestations are associated with the entry of the cercariæ into the skin, and consist of an irritative dematitis depending upon the intensity of exposure. Within a few hours minute petechiæ may be observed at the sites of invasion of blood vessels, but these disappear in a day or two.

B. mansoni inhabits chiefly the branches of the portal vein in the liver and the mesenteric veins. Its eggs, deposited within the submucous layer of the large intestine, give rise to dysentery-like symptoms, commencing six to eight weeks after infection ; mucus with blood is passed from time to time, the egg-laden stools becoming frequent and their passage being perhaps attended with tenesmus. In certain well-established cases small (sometimes large) branching, soft growths are felt inside the sphincter ani. (Fig. 141.) They resemble polypoid growths and are apt to be mistaken for internal piles. They may extend as high up the bowel as the sigmoid flexure. If one of these growths is torn up, the lateral-spined eggs are seen in the debris.

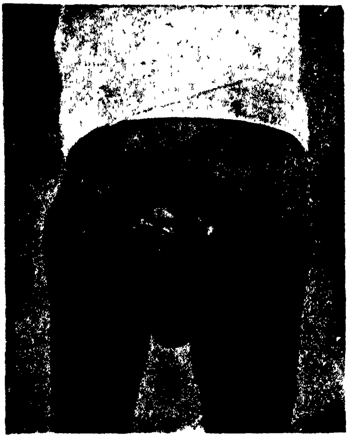


Fig. 141.—Rectal bilharziasis: adenomata prolapsed through anus. (*After Madden.*)

In heavy infections, in early cases, toxic symptoms resembling those of katayama disease (p. 700) are noted, especially in Europeans. General symptoms consist of intermittent pyrexia, with giant urticaria, abdominal pain, anorexia, rigors, and pulmonary symptoms. (Chart 27.) The very evident urticaria, often accompanied by swelling of the face and lips, is thought by some to be due to destruction of cercariæ in the skin capillaries ; by others to the filtering out of foreign proteins from the portal circulation. Pons stated that cough is invariably present in early cases, and tenderness is found over the liver, spleen, and intestines, especially over the cæcum. On abdominal examination of dysenteriform cases enlargement of liver as well as of spleen is frequently found. A pronounced leucocytosis with high eosinophilia (up to 76 per cent.) is invariable.

Later, localized symptoms, with passage of dysenteric motions, supervene.

In the terminal stages large palpable abdominal tumours may form, and intestinal stasis or distension may take place. Infiltration of the buttocks with eggs, leading to induration and fistulæ, is not uncommon. When the liver has become markedly cirrhotic, ascites may be present. Pneumonia from egg-deposition in the lungs is an occasional complication.

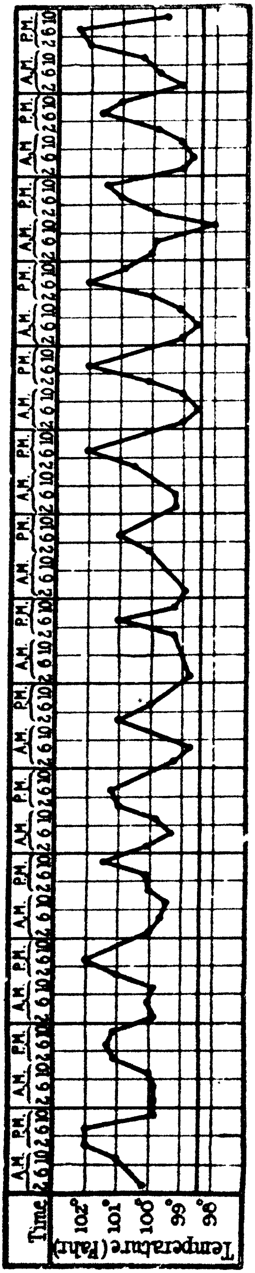


Chart 27.—Four-hourly temperature chart of acute bilharziasis (*B. mansoni*). (*Lawton.*)

Sometimes dysenteric attacks may develop into acute diarrhœa, of choleraic type, which may prove fatal. Deposition of the eggs in the appendix occurs comparatively often and produces symptoms of a subacute appendicitis. Generally the organ is much thickened and infiltrated so that it can easily be palpated. The diagnosis of bilharzial appendicitis from septic or amœbic appendicitis may be difficult.

Symptoms of the hepato-lienal form (Egyptian splenomegaly).—The symptoms of this condition, commonly known as "Egyptian splenomegaly," appear to be more objective than subjective. There are irregular fever, wasting, and a striking pallor. The spleen is obviously enlarged, hard and firm, often reaching to the umbilicus (Fig. 142); the liver also in the early stages is enlarged. Vomiting and diarrhœa are frequent. In the later stages œdemas, of varying degree, and purpuric rashes may ensue. The fever is generally irregular, intermittent, and not amenable to quinine. The splenic enlargement causes pain and discomfort, especially after meals, and on exertion gives rise to a dragging sensation, though the main symptoms are caused by debility and anæmia. As the disease progresses, so pyrexia increases, until the steady enlargement of the liver and spleen causes the costal angle to expand. Hæmatemesis often occurs, but jaundice is rare. The final stage is ushered in by cirrhotic changes in the liver, which becomes hard and firm and shrinks within the costal margin. The spleen also becomes fibrotic, but does not proportionately decrease in size. The pain, which is due to perisplenitis and perihepatic adhesions, increases, while vomiting is common. Finally, the patient succumbs with symptoms of hepatic cirrhosis, ascites, and emaciation. Death is usually due to pulmonary complications.

Kenawy described a continuous venous hum which may be heard by the stethoscope over the liver, and which he considers is characteristic. The hum becomes louder during inspiration, and also in the erect position. After splenectomy the sound disappears ; this is probably due to the removal of some venous communication. Unfortunately, this sign is of no great assistance in differential diagnosis, for a similar hum has been noted in other forms of cirrhosis, as well as in Banti's disease.

The blood picture varies. In the early stages there is a leucocytosis of 17,000 and myelocytes may be present ; later, progressive anæmia of the microcytic type becomes apparent, with leucopenia of 3,000 and a mononuclear increase of 10–17 per cent.

Among the rarer complications, thrombosis of the portal vein and hepatic carcinoma have been recorded.

The course of the disease is generally protracted: in older children and adults it may run twenty years or more. Ascites is always regarded as unfavourable. In all its aspects this stage resembles bilharziasis japonica.

Diagnosis. — The characteristic eggs are easily found in the fæces under low powers of the microscope ; they may be very scanty, and it is necessary to examine three or more specimens before arriving at a negative diagnosis. (Fig. 143). They are more easily found in solid than in fluid stools, especially in the outer portions of a motion. Quite a high proportion of cases are latent—that is to say, they do not present any recognizable or urgent symptoms. The Editor found examination of mucus and scrapings from the rectal mucosa, obtained through the proctoscope or sigmoidoscope, more reliable than a fæces examination. Allen Scott also considered that the highest diagnostic efficiency is obtained by rectal swabs. On examination of over 1,000 fæcal specimens by three different techniques and by a combination of them—*viz.*, egg-counting by Stoll-Hausheer method, using 0·005 c.c. of fæces diluted in decinormal soda, sedimentation in normal saline consisting of concentrated egg-count and swabs—he found that the latter method gave the best results. In about 5 per cent. of cases in Egypt the characteristic eggs may be found in the urine as well as in the fæces.

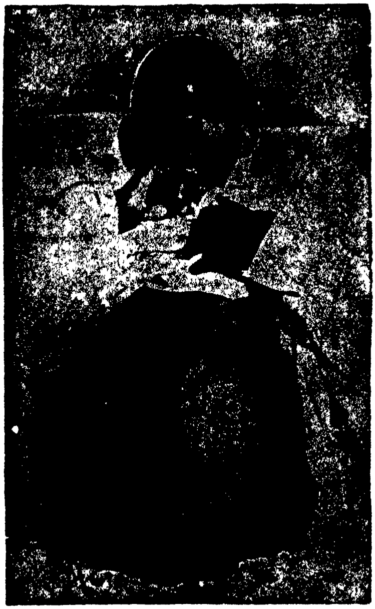


Fig. 142. — Egyptian splenomegaly. (*After Richards and Day ; by permission of the British Journal of Surgery.*)

Fülleborn recommended the Telemann method of finding the eggs when scanty. The fæces are shaken up with a mixture of concentrated hydrochloric acid, 1 part, water, 1 part, ether, 2 parts, and strained through gauze; the filtrate is centrifuged and examined. The deposit may then be mixed with water and the eggs encouraged to hatch, when the miracidia are more easily detected (Appendix, p. 1009).

In this form of bilharziasis the total serum proteins do not vary much from normal, but the globulin and globulin-albumin rates and the percentage of euglobulin are increased, more especially in patients with splenomegaly (Khalil and Hassan). The formaldehyde test may, therefore, constitute a reliable means of differentiation from leishmaniasis.

The complement-fixation and intradermal tests are the same as in *B. hæmatobia* infections (p. 683).

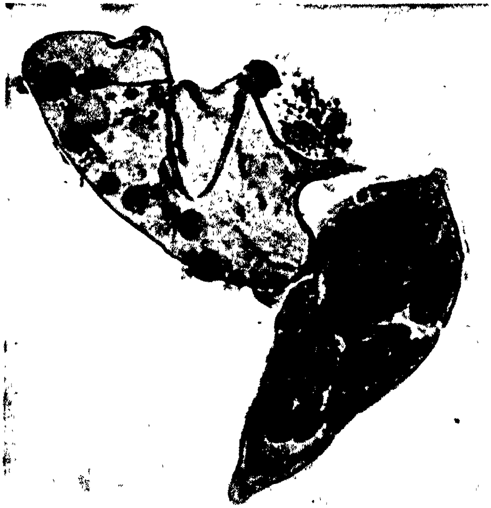


Fig. 143.—Microphotograph of miracidium of *Bilharzia mansoni* escaping from egg. × 1,500. (*Dr. A. J. Chalmers.*)

In rectal disease, should *B. mansoni* be suspected, an adenomatous growth may be removed by forceps and examined for eggs.

Sigmoidoscopic examination usually reveals pedunculated adenopapillomata in the upper part of the rectum, but usually this is unnecessary, as they can be felt by digital examination and may sometimes be seen protruding in polypoid masses from the anus. In very early cases granular patches can be detected on the rectal mucosa from which eggs may be obtained by scraping with a blunt Volkmann spoon through the sigmoidoscope. The localized thickenings of the large intestine, due to polypi and pericolic growths in the transverse and pelvic colons, may be palpated in heavily infected subjects.

Differential diagnosis of the hepato-lienal form has to be made from splenic anæmia and other forms of splenomegaly. It is stated that injections of adrenalin decrease the size of the spleen in splenic anæmia, but are without effect in bilharziasis.

TREATMENT

I. Antimony treatment.—Gross changes in the organs are more extensive than in *B. hæmatobia* infections, due partly to toxic absorption and partly to deposition of eggs, and it is possible, as Madden and Day asserted, for adult trematodes to be extirpated by tartar-emetic without affecting the fibrotic changes. Hence, it may prove necessary to remove polypoid or adenomatous growths obstructing the intestines. In early cases antimony is as successful as it is in *B. hæmatobia* infections. Lampe in Surinam treated out-patients with three injections of 3 c.c., 5 c.c. and 7·5 c.c. of a 1 per cent. solution of tartar emetic thrice weekly—a total of 150–200 c.c.—the whole course occupying six to seven weeks. Dye and others gave rectal injections of tartar emetic as being especially suitable for children, who can tolerate 16 gr. by the rectum without toxic effects, but the amount of the drug absorbed is unknown. Five to seven daily intrarectal injections are necessary.

B. mansoni is more difficult to exterminate than *B. hæmatobia*, and requires larger doses of intravenous tartar emetic—up to a total of 50 gr. As in *B. hæmatobia* infections, fouadin has been extensively employed as an intramuscular injection, especially in Egypt, but it does not appear to be as efficacious as intravenous tartar emetic, while Khalil reported a few cases of sudden death. From Egyptian statistics in 1934, it is learned that the total number of bilharzia cases which received nine or more injections of fouadin was 1,938 ; of these 53 per cent. were cured, but 21 per cent. required eleven injections, and the remainder even more. After thirteen injections, signs of intolerance were noted. (*See* p. 685.)

Khalil thought that there are individual variations in the excretion of fouadin, and that idiosyncrasies to this drug may occur. The rate of renal excretion is important, and the drug is most easily tolerated by children. Any degree of kidney damage is a contra-indication. Usually, after the fifth injection dead eggs of *B. mansoni* may be found in the fæces. Relapses are recorded in 33 per cent. of cases. Fouadin gives a positive catechol test in the urine—a green colour with ferric trichloride which changes to violet on adding sodium carbonate. If the urine is not clear, it must be centrifuged. Anthiomaline, as in *B. hæmatobia* infections, is now being extensively employed with success (p. 686).

II. Emetine.—Emetine is as efficacious in this disease as it is in *B. hæmatobia* infections. The amount necessary, according to Maciel, is about 0·6 grm. (9·2 gr.) in a series of ten injections. The initial two injections should be ½ gr. each, the remainder 1 gr. Emetine should be reserved for those who are intolerant of tartar emetic.

III. Operative treatment of intestinal bilharziasis.—Dolbey and Fahmy held that the rational method of obtaining a permanent cure in cases with extensive disease of the rectum is excision of the whole tube of mucous membrane. Lengths of 12–15 in. can be removed with ease. A circular incision is made at the junction of skin and anal mucous membrane; the external sphincter and levator ani attachment are separated by blunt dissection ; when once the latter has been separated, the mucous tube may be loosened by the gloved finger and withdrawn until the upper limit of the papillomata is reached. Recovery is uneventful ; there is little tendency to retraction of the tube, and control of the anal sphincter is regained. This operation is unsuitable for very anæmic or debilitated patients.

IV. Operative treatment of the hepato-lienal form.—According to Richards, palliative operative interferences, such as frequent tapping and the Talma-Morrison operation (omentopexy), are permissible in cases with ascites, though in early cases before the development of ascites, he performed splenectomy with success. Coleman, Bateman and Stiven confirmed the value of this operation. The mortality-rate is about 15 per cent. and deaths are due to late shock. Great care is still necessary in the selection and preparation of cases for operation. Ascites, pellagra, heart disease and debility are contra-indications. Considerable leucocytosis should be considered a bar to operation, and it is necessary to differentiate this condition from leukæmia. An injection of pneumcoccal vaccine should be given the night before the operation to prevent the possible development of pulmonary complications. In his account of 390 cases, Stiven stated that five to six weeks' preliminary treatment is necessary ; it should consist of carbon tetrachloride, to get rid of intestinal parasites, and intravenous injections of neo-salvarsan for syphilis. The weight of the spleens removed by this surgeon averaged 3¾ lb. The favourable results appear to be permanent, and ascites does not develop. Day claimed that early cases are curable with tartar emetic.

Stiven operated with stovaine spinal anæsthesia, making an incision, varying in length with the size of the spleen, down the centre of the left rectus parallel with the middle line, and starting at the costal margin. Skin and rectal sheath are divided by the knife, the rectus muscle being separated into two equal parts by a sweeping action of the finger. The peritoneum being opened, the spleen can be delivered, in the absence of adhesions, through the wound. The pedicle is clamped and the organ removed. The former is now transfixed with a long pedicle needle armed with black and white linen thread, linen being less apt to slip than silk, and the difference in colour ensuring recognition of the necessary interlocking. After operation, patients are given nothing to drink for twelve hours and then strict diet for five days, and subsequently a purge. Nourishing diet and iron and arsenic are necessary. Patients usually leave hospital after fifteen days.

Prognosis.—This is the same as for *B. hæmatobia*, but it must be remembered that this disease is generally latent, and that even large intestinal polypi may give rise to little or no inconvenience.

Cases with papillomata of the rectum, dysenteric symptoms, tenesmus, and anæmia, and those with actual obstruction of the intestinal canal and cirrhotic changes in the liver, must be regarded as serious.

Prophylaxis is the same as in *B. hæmatobia* (p. 687). There appears to be a greater probability of contracting the disease in the neighbourhood of canals and waterways, which are the favourite haunt of *Planorbis boissyi*, of which a high proportion (50 per cent. or more in some cases) are found to be infected with the cercariæ of this trematode in Egypt. In northern Nigeria and in Kenya, infection has been recorded from bathing in clear pools in the absence of any obvious aquatic vegetation. In South America and Venezuela prophylaxis is concerned mainly with avoiding collections of water and cane-field irrigation canals which form the haunts of *Australorbis glabratus*.

III. Eastern Bilharziasis (*Bilharzia japonica*)

Synonym. Katayama Disease. Schistosomiasis japonica.

Definition.—A chronic endemic disease of Eastern Asiatic countries, caused by *Bilharzia japonica*, and characterized by great enlargement of the liver and spleen and ascites. The eggs of the parasite are discharged in the fæces. Initial toxic symptoms, urticaria and pyrexia, are common.

History and geographical distribution.—For very many years an endemic disease characterized by splenomegaly, enlargement of the liver, cachexia, ascites, pyrexia, and dysenteric symptoms had been observed in Japan. In 1888 Majima found eggs in a cirrhotic liver, and in 1904 Katsurada saw a miracidium emerge from similar eggs which he had found in fæces; later, he discovered the adult trematode, *B. japonica*, in the portal veins of the cat. In that year also Catto found similar parasites in a Chinaman in Singapore. The next addition to knowledge was made by Katsurada, who succeeded in communicating the parasite to cats by immersing their legs in the water of certain ponds reputed to convey the disease. In 1913 Miyairi and Suzuki traced the parasite, through snails common in the infected districts, back to the vertebrate host, a discovery confirmed in the following year by Leiper and Atkinson.

So far, the parasite had been found principally in Chinese and Japanese, though a few Europeans—mostly naval officers and sportsmen, addicted to snipe-shooting in the rice-fields—had acquired the disease. Its present range, as far as is known, may be stated as follows: In China it occurs in endemic foci in the Yangtse basin, from Ichang, 350 miles above Hankow, to the sea; in the provinces of Hunan (Siang River), Hupeh, Anhwei, Kiangsu and Kiangsi. An endemic centre has recently been reported from Shiuchow, on the North River near Canton, and also from Foochow (Fukien). It has been recorded on the Burmese border between Yunnan and the Northern Shan States. In Japan it is especially prevalent in the province of Hiroshima and in the village of Katayama. Endemic foci also exist in Southern Formosa, and in the Southern Philippine Islands—Samar, Leyte, Mindanao and in Celebes (Dutch East Indies.) (Map. V.) In countries where it exists, dogs, cats, rats, and imported cattle and horses are found naturally infected: native cows, on the other hand, appear to be immune.

Ætiology.—The *parasite* closely resembles *B. hæmatobia*, though it is smaller and the integument is smooth and non-tuberculated. In proportion, the acetabulum or ventral sucker is longer and stouter than in either *B. hæmatobia* or *B. mansoni*. The *eggs*, smooth and slightly oval, measure 0·08 mm. by 0·06 mm., and pass through the intestines into the fæces. They possess a rudimentary lateral spine, and show considerable variation in size, but in the uterus of the female bilharzia they are much smaller than those in the fæces. (*See* p. 893.)

The miracidium, after casting its cilia, develops in fresh-water molluscs of the genus *Oncomelania*[1], Gredler, 1881, which has a widespread distribution in Japan and China; probably all species of this genus are potential carriers of *B. japonica*.

---

[1] There has been much confusion about the correct nomenclature of these snails; the reader is referred to Appendix, p. 895.

Pathology.—The outstanding feature is the great enlargement of the liver and spleen. The former is hypertrophied and nodular, due to the formation and contraction of fibrous tissue; on digesting with 3 per cent. potash solution, it is found to contain many eggs. The great enlargement of the spleen, on the other hand, is probably due to absorption of toxins or, possibly, to back-pressure, as eggs are seldom found there. As in other forms of bilharziasis, granules of black pigment are found in both viscera. The appendices epiploicæ are greatly thickened and may be matted together; the mesenteric and retroperitoneal lymph-glands are enlarged; hypertrophy and thickening of the lower parts of the intestinal tract, with formation of ulcers and polypoid growths filled with eggs, are generally noted. The bladder is unaffected.

Occasionally, indurations of the pia mater and granulomatous lesions of the cerebral cortex have been found, eggs being present in great numbers. The young forms of the parasite enter the general circulation through the veins and collect in the lungs, apparently entering the liver by traversing the mediastinum and the diaphragm. Inside the portal system they soon reach maturity. Infection of the fœtus during intra-uterine life is apparently possible.

Symptoms.—The disease produced by *B. japonica* is serious and, when pronounced, sooner or later proves fatal. The gravity of any given case depends, amongst other things, on the degree of infection and the circumstances of the patient. Of 1,077 persons near Shushima, Japan, examined by Koiki, 42 were found infected. Of these, only 22 were not in good health. Penetration of the skin by the cercariæ causes an intense pruritus, partly mechanical, and partly due to an irritating substance secreted by the larvæ. The erythema thus produced was formerly regarded by the Japanese as a skin disease, "kabure." The same condition is produced by infection with cercariæ of the other two human species—*B. mansoni* and *B. hæmatobia*.

The course of the disease can be divided into three stages: *invasion*, *deposition* and *fibrosis*. The *first* (Katayama disease) occurs shortly after infection and lasts about a month. It is associated with toxic symptoms—pyrexia, giant urticaria, abdominal pain, paroxysmal cough, leucocytosis, and a high eosinophilia (60 per cent. or more). Dermatographia is common. The *second* is characterized by great emaciation and is accompanied by dysenteric symptoms and enlargement of liver and spleen. The *third*

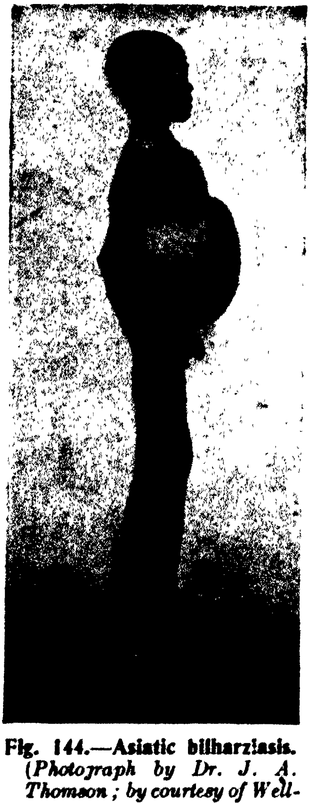


Fig. 144.—Asiatic bilharziasis. (*Photograph by Dr. J. A. Thomson; by courtesy of Wellcome Bur. Sci. Res.*)

or final stage, when it does supervene, occurs from three to five years after infection. In this the liver and spleen are cirrhotic and enlarged (hepato-lienal fibrosis). Ascites and œdema of the extremities appear, with anæmia and exacerbations of dysenteric symptoms (Fig. 144). The patient may die of exhaustion, of some terminal infection, or of Jacksonian fits, hemiplegia, and even total blindness owing to deposition of eggs in the cerebral cortex, or destruction of the visual centres.

Diagnosis.—All cases of urticarial fever from the endemic districts should be watched for many months (especially if eosinophilia persists after the subsidence of the primary attack) and the stools examined for eggs of *B. japonica*. All cases of chronic intestinal disturbance from the districts mentioned, especially if associated with enlargement of liver and spleen, should be regarded as possible cases of bilharziasis, and the blood and stools should be examined. If the characteristic eggs (Fig. 145) are discovered definite diagnosis is established.

Complement-fixation reactions and intradermal tests as in *B. hæmatobia* infection, with antigen made from cercariæ, may be employed; and a similar reaction is obtained with extracts from the bodies of the adult trematodes when the serum of artificially-infected horses is used (Seuzasu, 1917). According to Faust and Meleney, the aldehyde or serum-globulin test is strongly positive in many cases.

It is said that ferments are given off by the adult bilharzia, one of which is allied to trypsin and digests albumin in an alkaline medium.

Fig. 145.—Eggs of *B. japonica* in fæces. × 250. (*Microphotograph by Dr. J. Bell.*)

The disease in its terminal stage has to be differentiated from Banti's disease and from kala-azar. Campbell states that most cases diagnosed as Banti's disease in the Far East are in fact bilharziasis japonica. Louchs suggested that a safe method of making a positive diagnosis is by biopsy of the liver during splenectomy, and the demonstration of the eggs, when they are not apparent in the fæces. Differential diagnosis has to be made also from Jacksonian epilepsy, cysticercosis and tumours of the brain, since deposition of *B. japonica* eggs in the cerebral cortex may give rise to granulomata of considerable size.

Treatment.—Antimony tartrate, given in the same doses and in the same manner as for *B. hæmatobia*, appears to be efficacious in killing adult trematodes. A total amount of 24 gr. or more is necessary. In two cases under the care of the Editor, Jacksonian fits disappeared after this treatment. According to Faust and Meleney, 20-30 gr. of intravenous tartar emetic over a period of eighteen to twenty days is usually curative. Kastein and others claimed that intramuscular injections of fouadin in doses up to 5 c.c. are effective, as in *B. hæmatobia* infections, but the full course, as detailed on p. 686, is necessary.

Unfortunately, in China and Japan patients usually apply for treatment only when in the advanced stages; in these the intestinal ulceration and hepatic cirrhosis are generally so pronounced that drug treatment is of little avail.

As in Egyptian splenomegaly (p. 697) splenectomy has been performed, but usually with little success, the hepatic cirrhosis being too far advanced. Campbell suggested that, if the blood-platelet count rises after the delivery of the spleen during operation, the splenic artery should be tied, and the spleen returned into the abdominal cavity, and that this procedure obviates operative shock.

Emetine.—Injections of *emetine hydrochloride* are as efficacious as in the other bilharzia infections; but it is necessary to remember that, as has been shown experimentally in goats infected with the allied *Bilharzia spindalis*, fatal verminous thrombosis of pancreatic and portal veins, as the result of the presence of dead parasites, may ensue.

Prophylaxis.—Water reported to cause the disease should be boiled, or avoided, for drinking or bathing purposes. Sportsmen, if they must frequent such regions, should wear rubber boots or waders. According to Narabayashi, lime in a solution of 1 in 1000 is the most economical reagent for the extermination of the intermediary host (*Oncomelania*), and kills cercariæ in thirty minutes. It is especially recommended because of its added value as a fertilizer. Miyajima advocated damming up ditches for twenty-four hours and the addition of quicklime to make up a 1 per cent. solution. For liquid mud the application of a steam jet is said to be effective. Copper sulphate, 1 in 200,000, is toxic for snails, but they may also be kept in check by training coolies to collect them. It is said that eggs remain viable for ten days outside the body in solid fæces, and this factor should be recognized in formulating sanitary measures. Mass treatment in out-patient clinics will help to eliminate carriers of the disease, whilst educational propaganda, especially in China, is all-important. The prophylaxis of this form of bilharziasis presents many difficulties, for the disease attacks domestic animals, especially dogs, as well as man. The snail vectors, moreover, live in almost inaccessible situations in channels, overhanging banks and ditches, and, being operculated, can withstand drought with impunity. It has been shown by Rose that those snails which are heavily infected do not propagate, as infection with cercariæ destroys the genital glands.

CHAPTER XLII

PARASITES OF THE LYMPHATIC SYSTEM AND CONNECTIVE TISSUES : FILARIASIS

Definition.—Morbid conditions produced by certain nematode worms, or filariæ, the adults of which, of both sexes, live in the lymphatics, connective tissues or mesentery, producing live embryos, or microfilariæ, which find their way into the blood-stream where they are capable of living for a considerable time without developing further.

History.—In 1863 Demarquay found what is now known as the embryonic form—microfilaria bancrofti (Fig. 146, *1*)—in hydrocele fluid, and in 1866 Wucherer discovered the same organism in chylous urine. In 1872 Lewis established the fact that the organism lives principally in the blood of man, and consequently named it *Filaria sanguinis hominis.* The adult form was found in 1876 by Bancroft in Brisbane, and named *Filaria bancrofti* by Cobbold.

Manson in 1878 made the important observation that the mosquito subserved the parasite as intermediary host, and in 1880 described the remarkable phenomenon of filarial periodicity. Originally, Manson proposed to call the embryonic form of *Wuchereria bancrofti*, in order to emphasize its nocturnal periodicity, *Filaria nocturna*, but, in accordance with the rules governing zoological nomenclature, precedence was given to Cobbold's name for the adult form ; the embryonic form is therefore referred to in this manual as microfilaria bancrofti ; the other filariæ of the blood are named microfilaria loa (or mf. diurna) (Fig. 146, *2*), microfilaria malayi (Fig. 146, *3*), microfilaria volvulus (Fig. 146, *4*), microfilaria ozzardi (mf. demarquayi) (Fig. 146, *6*) and microfilaria perstans, the embryo of *Acanthocheilonema perstans* (Fig. 146, *5*). *Filaria bancrofti* has been renamed *Wuchereria bancrofti* and an allied species, *W. malayi*, has been discovered.

Pathological importance.—Only some of these parasites, so far as we know at present, have important pathological bearings, notably, *W. bancrofti* and *W. malayi*, which, in their adult stages, inhabit the lymphatics of man. There is abundant reason to believe that they are the cause of endemic chyluria, of various forms of lymphatic varix, and of other tropical diseases, including tropical elephantiasis. *Loa loa* and *Onchocerca volvulus* produce less serious pathological lesions.

The filariæ less important from a pathological standpoint are dealt with in the Appendix (pp. 735–738).

I. FILARIASIS DUE TO WUCHERERIA BANCROFTI

Geographical distribution and prevalence.—*Wuchereria bancrofti* occurs indigenously in almost every tropical and subtropical country, from Charleston in the United States and Southern Spain in Europe to Brisbane in Australia. It is extremely common in India and South China, Samoa, and many of the Pacific islands, where fully 60 per cent. of the inhabitants are affected. It is also found in the West Indies, South America, North Africa, Southern Sudan, West and Central Africa (Map VI).

If the individuals who exhibit the microfilaria in their blood be reckoned in addition to those who exhibit the pathological effects of filarial disease, but in whose blood the microfilaria is no longer to be found, the incidence of filarial disease in some of the Pacific islands is very high—as high as 80 per cent.

Ætiology. *Parental forms.*—The parent filariæ (*Wuchereria bancrofti*) have been found many times. They are long, hair-like, transparent nematodes, 2–8 in. in length (Figs. 147, 148). The sexes live together, often inextricably coiled about each other. Sometimes they are enclosed, coiled up several in a bunch and tightly packed, in little cyst-like dilatations of the distal lymphatics (Maitland); sometimes they lie more loosely in lymphatic varices; sometimes they inhabit the larger lymphatic trunks

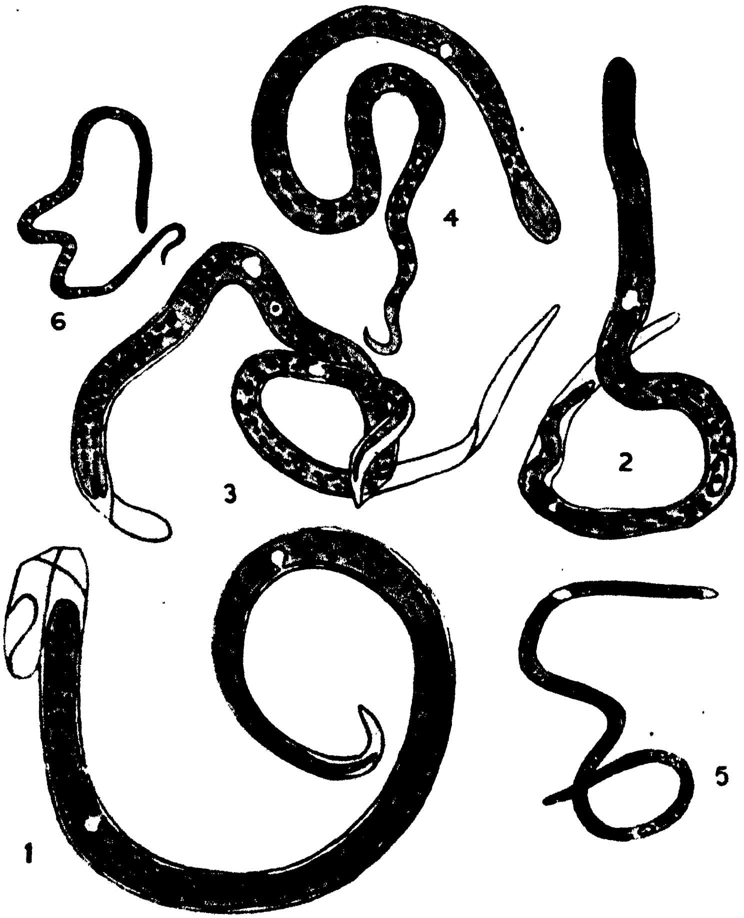


Fig. 146.—Human microfilariæ ; 1, Mf. bancrofti ; 2, Mf. loa ; 3, Mf. malayi ; 4, Mf. volvulus ; 5, Mf. perstans ; 6, Mf. ozzardi. (*Drawn to scale.*)

between the glands, the lymphatic glands themselves and, probably not infrequently, the thoracic duct.

The female worm is almost twice the length of the male, and considerably broader. The fully-mature and fecundated female filaria gives birth during her lifetime to an unending stream of living embryos, or microfilariæ, which emerge from the vaginal orifice. (For further details *see* Appendix p. 925.)

Opportunities have arisen for the study of the life history of *W. bancrofti* in over 1,000 marines who have returned to America from Samoa. After 3–6 months' residence there acute manifestations of filariasis resulted. Immature worms have been removed from fugitive swellings in the subcutaneous tissues, but so far no microfilariæ have been discovered in the blood. This is consistent with the view that it takes approximately one to one and a half years to complete development in the human body (Faust, 1944).

The life-spans of *W. bancrofti* and its microfilariæ have not been determined. From the fact that the microfilariæ have been found in the blood long after the opportunity of infection has passed, it is concluded that the adults may live for many years. The embryo filariæ sometimes disappear completely from the circulation within a few hours of the death of the parent worms during an attack of lymphangitis.

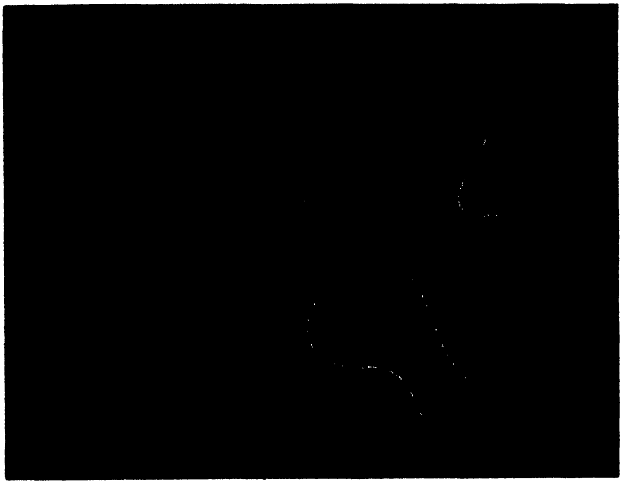


Fig. 147.—Wuchereria bancrofti (*enlarged*), *left, male ; right, female.* (*Dr. M. Oesterlein.*)

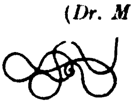


Fig. 148.—Wuchereria bancrofti (*natural size*), *left, male ; right, female.*

As shown by Wise and the Editor, the mature worm is cretified after its death, and may be found in this condition in the lymphatic vessels and glands, sometimes in large numbers (Fig. 150), and it has been found by the Editor originally, later by O'Connor and Elsbach, that the adult filariæ, whether alive or dead, cause occlusion of the lymph vessels and thereby contribute towards general lymph stasis.

According to O'Connor, microfilariæ are destroyed in the substance of the lymphatic glands and are responsible to some extent for the pathological changes found in these structures. He showed that they are broken up in the lymph-node sinuses; and that this is the common method of destruction of foreign substances in lymph-glands has been demonstrated by Indian-ink injection methods by Drinker, Wislieki and Field. McMullen (1937) described a case in an Indian, infected with *W. bancrofti*, in whom the microfilariæ were detected, by means of the slit lamp, in the anterior chamber of the eye. No visible eye lesions were present. (*See* p. 744.)

The microfilariæ.—When present in large numbers in the blood-stream, microfilariæ may be recognized in wet film preparations; but, when the parasites are scanty, or for the examination of a large number of persons, it is often necessary to examine a considerable quantity of blood (20 c.mm.) in thick-drop preparations, dried and then dehæmoglobinized. When seen in fresh blood the embryo filaria is a snake-like organism which, without materially changing its position, wriggles about very actively.

When dead and stained, the embryo is seen to be enclosed in a sheath (Fig. 150). On measurement, it is found to be 280 μ by 7 μ.

At the anterior extremity of the living microfilaria can be seen a minute spicule, which is shot out and as rapidly retracted, and it is thought by some that the head is sheathed by a serrated "prepuce." In a fresh blood preparation the spicule can be seen disturbing cells at some distance away. (Fig. 151.) The utility of this mechanism is not known. Manson, who observed a similar mechanism in other microfilariæ, including those of birds, suggested that they subserved a necessary function in periodicity—the microfilariæ being enabled to affix themselves to the walls of the capillaries by these means, thus enabling them to maintain their station in the blood-stream during the hours of daylight.

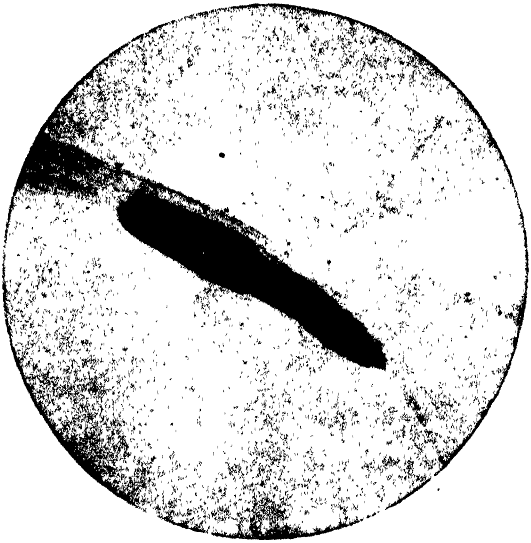


Fig. 149.—Calcified *Wuchereria bancrofti* lying in and blocking a lymphatic vessel.

Brug and Rodenwaldt described in the Dutch East Indies the embryo of a new filaria (*Wuchereria malayi*) which has a wide range in Malaya, Ceylon, India, Dutch East Indies, Indo-China, and South China

(Fig. 146, *3*). Development takes place in a number of mosquitoes of the genera *Mansonioides* and *Anopheles*. The adult stage of *W. malayi* was described by Rao and Maplestone in 1988.

Filarial periodicity.—A singular feature in the life of the microfilaria is what is known as " filarial periodicity." (*See also* p. 926.)

Fig. 150.—Microfilaria bancrofti in hydrocele fluid. The embryo on the right has escaped from its sheath.

If, under normal conditions of health and habit, the blood be examined during the day, the microfilaria is rarely seen, or, if it be seen, only one or two specimens at most are encountered in a slide. But towards evening they begin to appear in gradually increasing numbers. The swarm goes on increasing until about midnight, at which time it is no unusual thing to find as many as three hundred, or even six hundred, in every drop of blood ; so that it has been calculated that as many as forty or fifty millions

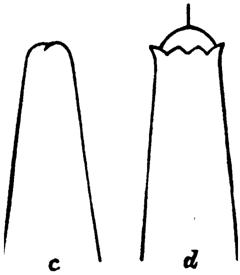


Fig. 151.—Structure of head end of Microfilaria perstans (*a, b*) and of Microfilaria bancrofti (*c, d*).

are simultaneously circulating in the blood-vessels. After midnight the numbers begin gradually to decrease; by eight or nine o'clock in the morning the microfilariæ have disappeared from the peripheral blood for the day. This nocturnal periodicity, under normal conditions, is maintained with the utmost regularity for as many as twelve years, as in the cases recorded by the Editor. Should, however, as Mackenzie has shown, a filarial subject be made to sleep during the day and remain awake at night, after a period of three to four days the periodicity is reversed; that is to say, the parasites come into the blood during the day and disappear from it during the night. It cannot be the sleeping state, as some have conjectured, that brings about this periodicity; for the ingress of the microfilariæ into the peripheral blood commences three or four hours before the usual time for sleep, and the egress several hours before sleep is concluded, and this egress is not complete until several hours after the usual time of waking. This night swarming of the embryos of *W. bancrofti* in the peripheral circulation has been regarded as an adaptation correlated to the life-habits of its liberating agent, the mosquito *Culex fatigans*, its usual intermediary host. (Chart 28.)

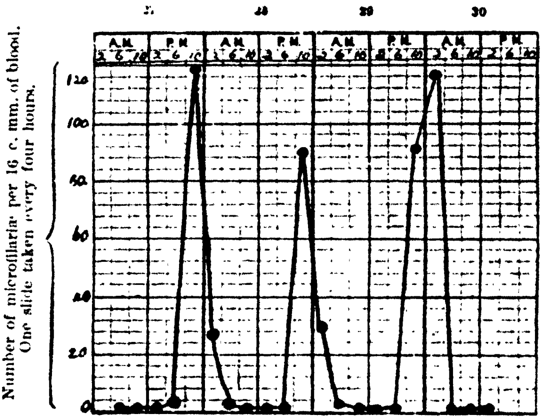


Chart 28.—Filariasis (*W. bancrofti*, Microfilaria nocturna), showing nocturnal periodicity.

This periodicity is maintained in the absence of the adult parasites, and is therefore a character inherent to the microfilariæ, as was demonstrated by Knott (1935) in a patient transfused with microfilariæ-containing blood and in whom they maintained nocturnal periodicity for fourteen days. Hawking's results (1940) were less conclusive.

Many years ago Manson had an opportunity of ascertaining that during their diurnal temporary absence from the peripheral circulation the microfilariæ retire principally to the larger arteries and to the lungs, where, during the day, they may be found in enormous numbers.

Low, the Editor and Walters showed that, though the periodicity curve is absolutely nocturnal, yet embryos may be present in small numbers in the peripheral blood in the daytime. The evening rise of the embryo filariæ is much more gradual than the matutinal fall, and the maximum migration occurs at 2 a.m.

A fall ensues, however, immediately the waking state is entered upon. The number of microfilariæ in an infected patient remains remarkably constant: Low and the Editor observed the periodicity curve maintained at the same level in one case for a period of twelve years.

Various theories have been advanced by Fülleborn and others to account for this singular phenomenon, though none are entirely satisfactory. Yorke and Blacklock thought that obstruction to the passage of microfilariæ through the cutaneous vessels is at a minimum at the end of the period of bodily activity, and that the periodicity is primarily dependent upon the variations in the actual supply of microfilariæ to the cutaneous vessels. But how account for the diurnal periodicity of microfilaria loa in circumstances which are exactly the reverse, or for the non-periodicity of the Pacific variety of *W. bancrofti*?

Clayton Lane believes that periodicity can best be explained by a process of periodic cyclical parturition on the part of the female filaria, with a daily destruction of all the embryos, and this hypothesis has received some support from the observation of O'Connor. He found that the uterus of the female adult filaria removed at operation empties its contents of microfilariæ at such a time that they are present in the blood-stream during the hours of night. The life-span of the individual microfilaria in the blood-stream has not been accurately ascertained but it is certainly several weeks, if not longer (*see* p. 925); and on a slide at 4° C. they have been kept alive for six weeks by the Editor. Kubo has actually shown that in *Dirofilaria immitis* of the dog there is also a seasonal variation, and that in China the maximal numbers of microfilariæ are found in the circulation during the hot weather at the end of August and beginning of September: the minimal numbers in November and December.

Non-periodic microfilaria bancrofti.—Formerly it was thought that nocturnal periodicity was uniformly observed by microfilariæ of *W. bancrofti* at all times and in every country. Many years ago Thorpe remarked that in Tonga and Fiji the microfilaria could be found often in great abundance in the blood during the day as well as in the night, but, strange to say, it has since been ascertained that the microfilariæ of neighbouring islands in the Pacific—namely, the Solomons, some parts of New Guinea and of the Bismarck Archipelago—are for the most part, though not entirely, periodic.

The Editor demonstrated that the microfilariæ of Indian immigrants who have acquired their filarial infections in India retain their periodic habits during at least three years of residence in Fiji, but that if an Indian or a Solomon Islander acquires the infection in Fiji the microfilariæ are non-periodic in habit.

As an explanation of this striking anomaly, it had been suggested that the non-periodic microfilaria is the progeny of a parent worm specifically distinct from *W. bancrofti*; but Leiper failed to find any anatomical difference between the Pacific worm and *W. bancrofti* of India, China, and South America. The Editor suggested that the non-periodic form constitutes a variety of *W. bancrofti* and proposed the name *var. pacifica* for this parasite, which produces certain pathological peculiarities. Fülleborn and the Editor, after minute study and comparison of the microfilariæ from these countries, found that they are morphologically identical. It had been suggested that the non-periodic habit of the Pacific microfilaria is a partial adaptation to the day-habit of the intermediary of the parasite in Fiji and other Pacific islands—*Aëdes variegatus* (*Stegomyia pseudoscutellaris*)[1]. O'Connor established the significant fact that the range of the non-periodic filaria is almost co-extensive with that of *Aëdes variegatus*, in the Pacific (*see* p. 975).

The habitat of microfilariæ.—In lung sections (Fig. 152) the microfilariæ lie outstretched or variously coiled in the vessels, large and small. In the heart-muscle they are found in the capillaries between the fibres; in the kidneys they seem especially to affect the Malpighian tufts; a very few are also found in the capillaries of the brain; vast numbers are present in smears from the inner surface of the carotid arteries. Preparations afford no explanation of how the microfilariæ contrive to maintain their position in the blood-current, or of the forces determining their peculiar distribution.

---

[1] Now known to entomologists as *A. scutellaris* (*see* p. 975).

Subsequent observations have shown that, though microfilariæ can be demonstrated in the capillaries of the liver and spleen in small numbers, the capillaries of the lung and kidney (Anderson) appear to be the favourite habitat of the embryos of *W. bancrofti* and of other species which do not exhibit this extraordinary nocturnal periodicity. Thus, the non-periodic Pacific microfilaria has also been found in greatest abundance in these situations.

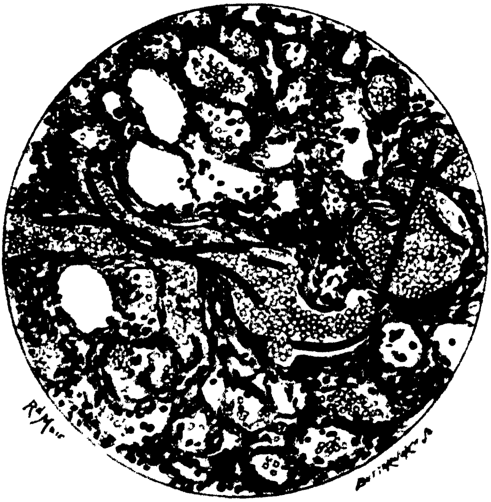


Fig. 152.—Section of lung showing microfilariæ in blood-vessels.
(*Microphotograph : Dr. Spitta.*)

The mosquito the intermediary host of W. bancrofti.—If the females of certain species of mosquito[1] (*Culex fatigans*[2] *or Aëdes variegatus*) which have fed on the blood of a filaria-infected person are examined immediately after feeding, the blood in the stomach will be found to harbour large numbers of living microfilariæ, while a few hours afterwards many of them will be seen actively endeavouring to escape from their sheaths. Change in the viscosity of the blood seems to prompt them to escape. After a time the majority succeed in effecting a breach and in wriggling themselves free from the sheaths which had hitherto enclosed them (Fig. 153). This process can be induced by chilling wet blood preparations on ice and then allowing them to thaw at room-temperature. The microfilariæ now, having become free, move about from place to place. At a somewhat later period it will be observed that, after discarding their sheaths, they have quitted the stomach and entered the thoracic muscles of the mosquito, where they may be seen moving languidly. To detect this, the insect should be dissected in normal saline solution, for, if distilled water is used, the larvæ break up. In the thorax of the insect the parasite enters on a metamorphosis which takes from ten to twenty

For a complete list of species which may serve as intermediary hosts, *see* Appendix, p. 928.

days (according to atmospheric temperature) ending in the formation of a mouth, an alimentary canal, and a peculiar trilobed caudal end, as well as in a relatively enormous increase in size (to $\frac{1}{16}$ in.) and activity. During this period the larva sheds its cuticle (ecdysis) twice. The larval filariæ now leave the thorax, and the majority pass forwards by the prothorax and neck, and, entering the head, coil themselves up close to the base of the proboscis beneath the pharynx and cephalic ganglia, though a few find their way into the abdomen, and even into the legs. Low first showed that the filaria, in its future progress, enters the proboscis, where, as pointed out by Grassi, its exact position is the interior of the proboscis-sheath (labium) (Fig. 154).

The parasites remain in the proboscis, awaiting an opportunity to enter a warm-blooded vertebrate host when the mosquito next feeds. This they appear to do by penetrating the thin membrane that unites the labella to the tip of the proboscis-sheath, and so pass on to the surface of the skin, which they penetrate in the neighbourhood of the puncture made by the mosquito. As pointed out by Annett and Dutton, there is a weak point in the chitinous skeleton of the labium just where the labella are joined on, and it is at this spot that the parasites escape. Sometimes the larval filaria, in its progress through the thorax, becomes arrested and dies; the defunct worm then appears to become enclosed, like a mummy, in a case of chitin inside the mosquito's body, resulting in the curious structure represented in Fig. 155. The physical conditions for development are important. The optimum is between 70 to 90° F. and 70–100 per cent. humidity. The highest infectivity rate is obtained when the microfilariæ in the imbibed blood number 100–150 in 0·2 c.c.

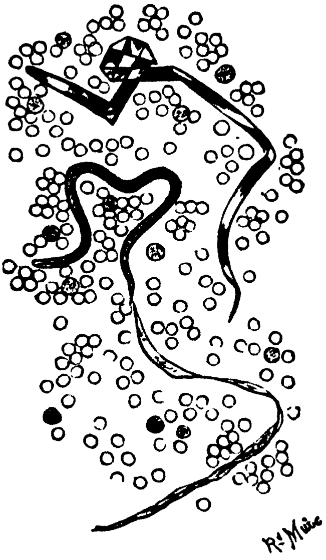


Fig. 153.—Microfilariæ casting their sheaths.

Mechanism of blood suction in mosquitoes.—Fülleborn concluded that blood-sucking in mosquitoes is a reflex action. The fluid is aspirated by the initiatory gulp-like working of the insect's sucking pump, and when the mouth cavity is full of fluid, the spasmodic action of the pump becomes converted into a more or less continuous flow until the abdomen is fully distended. This was later confirmed by Macgregor.

These observations prove that, like the malaria parasite, the filaria is introduced into its human host through the agency of a mosquito-bite. Once introduced into the human body, the filaria finds its way into the lymphatics and glands, where it attains sexual maturity; possibly, though no exact data are available, after a period of six months or more fecundation is effected, and in due course new generations of embryo filariæ (microfilariæ) are poured into the lymph. These, passing through the gland—if such should intervene—by way of the thoracic duct and left subclavian vein, or by the lymphatics of the upper part of the body, finally enter the circulation. (*See* footnote, p. 705.)

Epidemiology and endemiology.—In most countries in which filariasis is common it appears to be the rule that the incidence of infection is greatest in the male, though in British Guiana Daniels and Conyers found twice as many females infected as males. This exception to the general rule probably finds an explanation in the habits of the natives. The Editor's statistics from Fiji showed that of 1,320 people of Fijian blood, 30·4 per cent. of males and 23·9 per cent. of females were filariated.

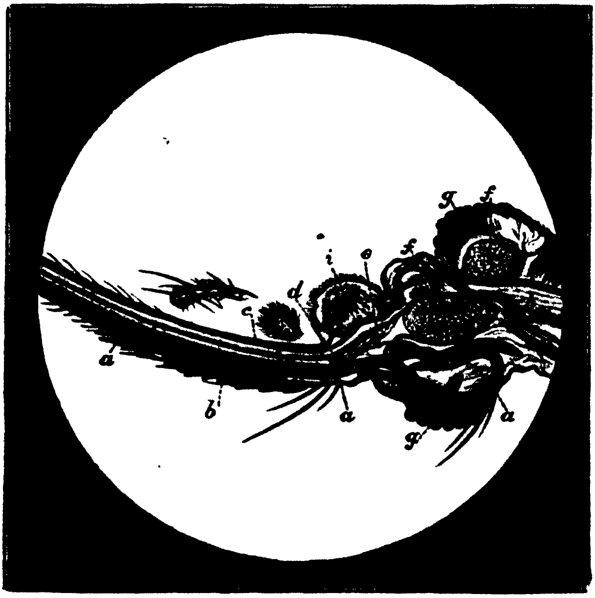


Fig. 154.—*W. bancrofti* **in head and proboscis of mosquito.** (*G. C. Low.*)

a, *a*, *a*, Filariæ; *b*, labium; *c*, labrum; *d*, base of hypopharynx; *e*, duct of veneno-salivary gland; *f*, *f*, cephalic ganglia; *g*, *g*, eye; *h*, œsophagus; *i*, pharyngeal muscle.

The incidence is greatest in both sexes after the twentieth year; comparatively more females than males are infected below the age of ten. The youngest infected patient—a child of 14 months—was recorded by Anderson in British Guiana. The rate of filariation varies considerably in different islands of the Pacific, even in different districts of the same island, and is in direct proportion to the incidence of elephantiasis and other filarial diseases. In 1912 in Ceylon the Editor found that, whereas 26 per cent. of the adults of some villages were infected, in neighbouring hamlets the inhabitants were quite free from these parasites and their associated diseases. Probably this inequality is mainly due to infections with *W. malayi*, and can be explained by proximity to tanks and pools where mosquitos breed.

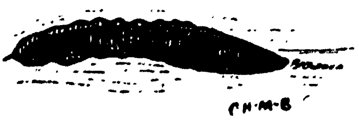


Fig. 155.—Chitinized filaria in thorax of mosquito.

Pathology.—*The filaria not generally pathogenic.*—In most cases of filarial infection the parasite exercises no manifest injurious influence whatever. In a certain proportion, however, there can be no doubt that it does exert a prejudicial effect, and this mainly by obstructing lymphatics. Healthy, fully-formed microfilariæ—that is to say, the embryonic filariæ in the blood—are, so far as we can tell, harmless.

Filarial disease originating in injury of lymphatic systems.—Roughly speaking, the filaria causes two types of disease: one characterized by varicosity of lymphatics, the other by more or less solid œdema. The exact way in which the parasite operates has not been definitely and absolutely ascertained for all types of filarial disease. Apparently, in some instances a single worm, or a bunch of worms, may plug the thoracic duct, and act as an embolus or originate a thrombus; or, the worm may give rise to inflammatory thickening of the walls of this vessel, and so lead to obstruction from the consequent stenosis or thrombosis. In other instances the minor lymphatic trunks and the glands may be similarly occluded. (Figs. 156, 157.)

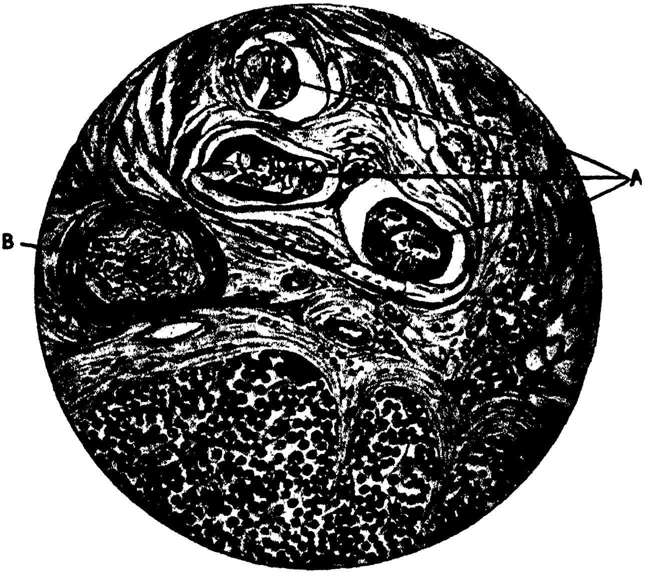


Fig. 156.—Section of a fibrosed lymphatic gland.

A, Portions of a calcified *W. bancrofti*: B, partially occluded lymphatic vessel.

The Editor demonstrated in Fiji that the afferent lymphatic glands situated at some considerable distance from the actual seat of the filaria worms (for instance, the lumbar glands) undergo considerable changes, such as fibrosis, focal necrosis and giant-cell formation. These changes may be due partly to the destruction of microfilariæ within the gland substance, or to toxins excreted by the adult parasites. Some microfilariæ undergo calcification, and thereby cause endothelial proliferative outgrowths in the lymphatic channels.

Pathology of lymphatic varix.—In consequence of the rich anastomosis between contiguous lymphatic areas, a compensatory lymphatic circulation is sooner or later established. But before this can be thoroughly effected a rise of lymph-pressure and a dilatation of the lymphatics in the implicated area must take place. This leads to lymphatic varix of different kinds, degrees and situations. When the seat of filarial obstruction is the thoracic duct, the chyle poured into that vessel can reach the circulation solely by a retrograde movement; this fluid may therefore be forced to traverse in a retrograde way the abdominal and pelvic lymphatics, the lymphatics of the groin, scrotum, and abdominal wall. As a consequence, these vessels, together with the thoracic duct up to the seat of obstruction, become enormously dilated. In dissection of such cases (Fig. 157) the thoracic duct has been found distended to the size of a finger, the abdominal and pelvic lymphatics forming an enormous varix, perhaps a foot in diameter and some inches in thickness, concealing kidneys, bladder, and spermatic cords. In such cases, when one of the vessels of the varix is pricked or ruptures, the contents are found to be white or pinkish. They are not limpid like ordinary lymph. They are chyle, therefore—chyle on its way to enter the circulation by a retrograde compensatory track. When the varix involves the integuments of the scrotum, the result is "lymph scrotum"; when most prominent in the groin, then a condition of glands is produced which Manson termed "varicose groin-glands"; when the lymphatics of the bladder or kidneys are affected and rupture from over-distension, then chyluria is the result; when those of the tunica vaginalis rupture, then there is chylous dropsy of that sac—"chylocele"; but when rupture is into the peritoneum—chylous ascites. Occasionally, varicose lymphatic glands resembling those in the groin are found in the axilla. Occasionally, also, limited portions of the lymphatic trunks of the limbs are similarly and temporarily, or more permanently, distended. This, doubtless, is the pathology of all those forms of filarial disease characterized by visible varicosity of lymphatics, with or without lymphorrhagia. It may happen that the obstruction is in some lymphatic tract on the distal side of the entrance of the chyle-bearing vessels into the receptaculum chyli. In this case a rupture of the consequent lymphatic varix will give issue to a limpid lymph unmixed with chyle.

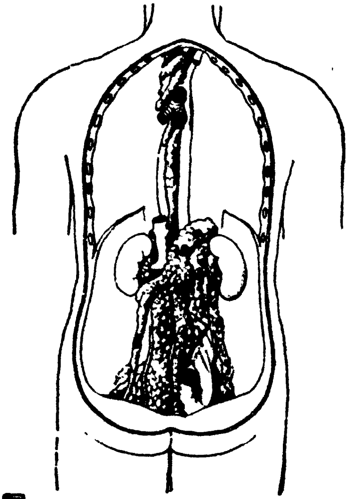


Fig. 157.—*Dissection of the lymphatics in a case of chyluria, showing the dilated right and left [illegible] and the thoracic* *Trans. Path. Soc.*

In filarial disease associated with lymphatic varix, microfilariæ are generally present in the blood as well as in the contents of the dilated vessels. Sometimes, it is true, the microfilariæ are not found. Such cases are probably of long standing; had the microfilariæ been looked for at an earlier stage of the disease, they would presumably have been discovered.

The microfilariæ have been seen to vanish from the blood-stream by several observers; doubtless this is due to the death of the parent parasite, and is generally associated with an attack of lymphangitis.

Pathology of elephantiasis.—*Reasons for regarding elephantiasis as a filarial disease.*—(1). The geographical distribution of *W. bancrofti* and that of elephantiasis correspond ; where elephantiasis abounds, there the filaria abounds, and *vice versa.* (2) Filarial lymphatic varix and elephantiasis occur in the same districts, and frequently in the same individual. (3) Lymph scrotum, unquestionably a filarial disease, often terminates in elephantiasis of the scrotum. (4) Elephantiasis of the leg sometimes supervenes on the surgical removal of a lymph scrotum. (5) Elephantiasis and lymphatic varix are essentially diseases of the lymphatics. (6) Filarial lymphatic varix and true elephantiasis are both accompanied by the same type of recurring lymphangitis. (7) As filarial lymphatic varix is practically proved to be caused by the filaria, the inference appears to be warranted that, with rare exceptions, the elephantiasis of warm climates—the disease with which lymphatic varix is so often associated and has so many affinities—is attributable to the same cause.

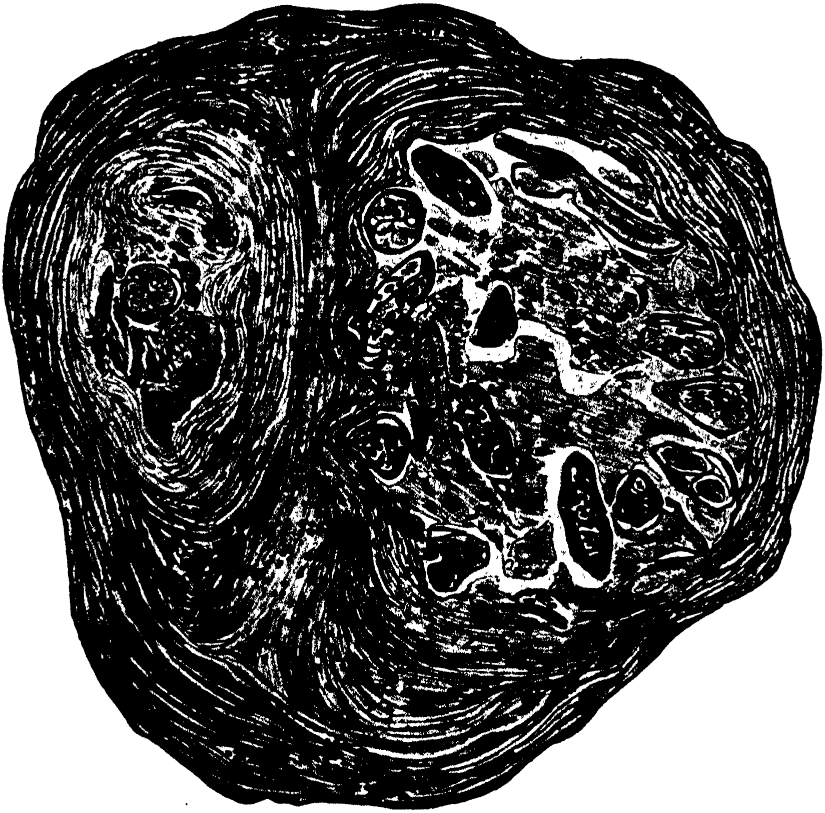


Fig. 158.—Section of a thickened brachial lymphatic containing portions of dead filariæ undergoing disintegration and blocking the lumen of the vessel. Note the large amount of fibrosis.

If the filaria be the cause of tropical elephantiasis, how account for the absence of the embryos from the blood, as is the case in the majority of cases ? The answer is: either the disease-producing filariæ have died; or the lymphatics draining the affected area are so effectually obstructed by the filaria, its products, or its effects, that any microfilariæ they may contain, or may have contained, cannot pass along these vessels to enter the circulation. Adult filariæ of both sexes in large numbers may be found in enlarged fibrosed lymphatic glands—epitrochlear, for example—without corresponding microfilariæ in the blood-stream.

We have already seen that in filarial lymphatic varix the parasites which produced the disease may die, particularly during attacks of lymphangitis; we have also seen that they may become cretified and may be found in large numbers in this condition or alive in the glands and lymphatic trunks, where, as the Editor has shown, they give rise to giant-cell formation and fibrotic obstructive changes (Fig. 158).

Furthermore, in filariated subjects a process of proliferation of the endothelium of the lymphatic vessels takes place—a species of lymphangitis, first described by the Editor and later confirmed by O'Connor; it is due to the action of the microfilariæ which become imprisoned in the endothelial lining of the vessel (Fig. 159).

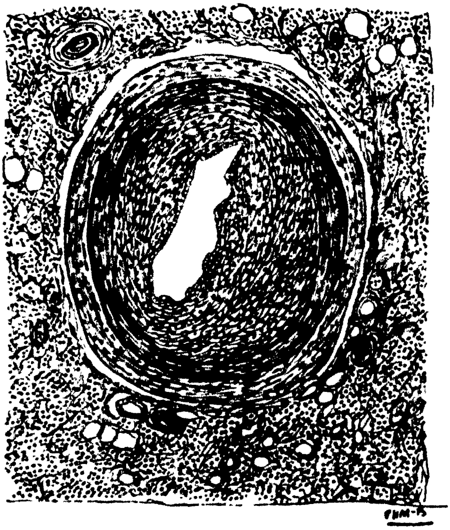


Fig. 159.—Occlusion of lymphatic vessels by proliferation of the endothelium in filariasis.

There is quite enough evidence to show that the true pathological basis of elephantiasis lies in the destruction and blockage of the lymphatic filters in the lymphatic glands.

For the true understanding of elephantiasis it is necessary to give a few facts about the known physiology of the lymphatic system. Lymph is a transudation from the veins and its production is maintained and regularized by intravenous pressure. It appears that, in order to produce true elephantoid tissue, a transudation of lymph must take place, and that this transuded lymph must contain an excess of protein; this forms an ideal culture medium for proliferating cells, thereby producing lymphous hyperplasia.

Superficial lymphatic capillaries are specially abundant and contain actively circulating lymph. The lymph stream flows in a series of directions from different areas of skin, with sharp lines of demarcation between each; therefore the former conception of a generalized lymphatic anastomosis is incorrect. Forming, as they do, the most important and extensive part of the lymphatic system, the superficial lymphatics show the most pronounced changes in the integument and subcutaneous tissues. Woollard and Gray demonstrated that the lymphatic supply of the skin is particularly rich, and that the vessels lie mainly in the superficial part of the dermis at a slightly deeper plane than the arterioles, which give off loops to the dermal papillæ. There is also a wide-mesh plexus of fairly straight vessels lying parallel to the skin surface, and these particular vessels contain no valves. In the deeper layers the lymphatics form a series of collecting radicles rather than a true plexus; they are joined to the superficial plexus by more or less vertically placed vessels, and the collecting trunks contain valves situated about 1 mm. apart. The deep fascia is devoid of lymphatics. There is, therefore, a clear separation of the superficial or external lymphatic system from the deep or internal system.

Diagnosis.—Diagnosis is made by demonstration of the microfilariæ in the night-blood; usually 20 c.mm. are necessary for the purpose, the thick-drop method being employed (*see* p. 999). But for reasons already stated the embryos may not always be present. There is usually an appreciable eosinophilia.

Serological and intradermal tests in filariasis.—These tests were introduced by Fairley, Taliaferro and Hoffman. The antigen is prepared from *Dirofilaria immitis* of the dog, which is washed and dried, it being estimated that 1 grm. is extracted from 250–300 worms. An alcoholic is more potent than a saline extract of the antigen. A positive complement-fixation is given with most cases of *W. bancrofti* filariasis; but it is a group reaction, and appears to be more reliable in *L. loa* than in *W. bancrofti*, but is also positive in *Onchocerca volvulus*. Lloyd and Chandra obtained the most reliable results with an antigen derived from the acetone-insoluble lipoids of *D. immitis* by the process used by Bordet for syphilitic antigen. Mohr and Lippelt obtained similar results with an antigen prepared from the filaria of the South American ostrich, *Contortospiculum rheæ*.

The intradermal test is based on the same immunological principles. Fairley uses 0·25 c.c. of a 0·1 per cent. extract as antigen. An immediate (30 min.) and delayed reaction are obtained; the latter may become indirect after a period of forty-eight hours. A wheal over 2 cm. in diameter is regarded as positive.

Technique. *Preparation of antigen for complement-fixation test.*—Technique similar to that described for bilharzia cercarial antigen is employed, 0·5 grm. of the dried powdered *Dirofilaria immitis* being extracted with 50 c.c. of 98 per cent. alcohol for 24 hours at 37° C. Well shaken by hand several times during this period, it is filtered through Whatman No. 1 and a Buchner filter. The filtrate is subsequently concentrated by bubbling air through the solution kept at a temperature of 40° C. by immersion in a water-bath till turbid; this turbidity is then removed by adding 8 c.c. of fresh alcohol, making the total volume 25 c.c. The resulting extract is then stored in the ice-chest in amber-coloured ampoules of 1 c.c. capacity. The technique of putting up the test is similar to the standard advocated for serological diagnosis of bilharziasis.

Preparation of antigen for intradermal test.—Fifty c.c. of a 1 per cent. saline extract of dried powdered antigen is incubated for two hours at 37° C., being well shaken by hand from time to time. Subsequently it is passed through a Whatman No. 1 filter paper, then through a Buchner filter, and is then sterilized

by passage through a sterile Seitz asbestos filter. The filtrate is put up in dark glass ampoules and stored on ice.

Pandit's reaction is an adhesion phenomenon. When blood containing microfilariæ is mixed with blood from a normal person and kept at room temperature for an hour or longer, the embryos become sluggish and surrounded by adherent leucocytes.

Filarial elephantiasis.—The anatomical situation of elephantiasis depends upon the distribution of the afferent lymphatic vessels. It must not be thought, however, that lymphatic elephantiasis is *solely* the product of filarial infection. The following classification of elephantiasis has been suggested by the Editor:

(*a*) Congenital or familial elephantiasis (Milroy's or Meige's disease); stenosis of main lymphatic trunks.
(*b*) Parasitic elephantiasis: *Wuchereria bancrofti*, *W. malayi*, or *Onchocerca volvulus*.
(*c*) Septic elephantiasis (*Elephantiasis nostras*—lymphatic infection by streptococci).
(*d*) Toxic elephantiasis due to absorption of irritating toxins, such as chrysarobin.
(*e*) Obstructive elephantiasis, due to tuberculous glands, carcinomatous growths, syphilis, or yaws, or to surgical removal of main lymphatic glands.
(*f*) Venous elephantiasis, secondary to venous thrombosis, such as *phlegmasia alba dolens*, or white leg.

Tesch, Brug and others have shown that elephantiasis is also produced by *Wuchereria malayi*. The difference between the two forms of lymphatic obstruction seems to lie in the predilection of this parasite for the legs rather than for the genitalia and scrotum as in *Wuchereria bancrofti* infestation.

In most cases the real origin of the obstruction lies in the fibrotic changes induced by the parasite in the lymphatic vessels and glands, leading to elephantiasis. Lymph stasis in lymphatic vessels alone does not produce elephantiasis; this has been proved by ligature of the lymphatic trunk, which results in œdema, but not in true elephantoid hypertrophy.

Anderson believed that the adult filariæ living in the lymphatic system, by the damage they produce in the intima of the vessels, so prepare the way that a streptococcal or staphylococcal infection, however mild, is able to contain a foothold and that by the changes thus produced the lymph-channels become further occluded.

O'Connor demonstrated that in filarial lymphangitis focal spots can be distinguished from which the inflammatory process commences, and that this indicates the site of a dead filaria; furthermore, that an attack of lymphangitis may be cut short by injection of sulpharsphenamine (0·2 grm. dissolved in 2 c.c. of sterile 1 per cent. novocain). This observer, with Golden and Auchincloss, found that in filariated subjects, especially in elephantiasis, calcified filariæ may be demonstrated by X-rays. The shadows range from 1 mm. in width to 2–3 mm. in length. This seems to

indicate that the infection may be quite extensive. Fifteen shadows, or groups of shadows, were detected in one elephantoid leg.

Thus can be explained the production of elephantiasis by the filaria, and the absence from the blood of the embryos of the parasite which started the disease, as they cannot pass the occluded glands. Very likely the parent worm, or worms, die at an early stage of the disease, killed by subsequent lymphangitis, or some other undetermined cause.

This anomaly is found in other conditions produced by *W. bancrofti.* In Fiji, for instance, the Editor observed that 38·2 per cent. of the cases of elephantiasis harboured microfilariæ, while the microfilaria-rate in glandular enlargement, also of filarial origin, was 34·6 per cent. On examining all those with clinical manifestations of filarial disease, it was found that 19·7 per cent. thus affected had microfilariæ in the blood. but that 44·8 per cent. of those with numerous microfilariæ showed no obvious sign of disease. As in the case of *W. malayi*, it is possible that the non-periodic *W. bancrofti* in the Pacific produces its own peculiar pathological picture. This filaria lives mostly in the lymphatic glands and produces phenomena which are connected with these structures. It has a special preference for the epitrochlear glands, and is therefore likely to produce elephantiasis of the arms. It does not produce either chyluria or lymphuria as does the periodic *W. bancrofti.*

SYMPTOMS, DIAGNOSIS, AND TREATMENT OF FILARIAL DISEASES

Enumeration of filarial diseases.—The diseases known to be produced by or associated with *W. bancrofti* are—abscess ; lymphangitis ; arthritis ; synovitis ; abscess of hip-joint ; varicose groin glands ; varicose axillary glands ; lymph scrotum ; cutaneous and deep lymphatic varix ; orchitis ; funiculitis ; hydrocele ; chyluria ; elephantiasis of the leg, scrotum, vulva, arm, mamma, and other parts ; chylous dropsy of the tunica vaginalis ; chylous ascites ; chylous diarrhœa, and probably other forms of disease depending on obstruction or varicosity of the lymphatics, or on the death or injury of the parent filariæ in a lymphatic abscess—including fatal peritonitis and secondary infections by pyogenic micro-organisms (filarial abdomen).

Abscess.—Occasionally, as already mentioned, whether in consequence of blows or other injuries, of lymphangitis, or of unknown causes, the parent filariæ die. Generally the dead body is absorbed, just as a piece of aseptic catgut would be, or becomes cretified.[1] Sometimes the dead worm acts as an irritant and causes abscess, in the contents of which fragments of the filaria may be found. Such abscesses, occurring in the limbs or scrotum, will discharge in due course or may be opened ; if properly treated surgically, they may lead to no further trouble. Should they form in the thorax or abdomen, serious consequences and even death may ensue.

The starting-point of these abscesses is, possibly, a small hæmorrhage produced by the filaria worm which becomes secondarily infected, but

by passage through a sterile Seitz asbestos filter. The filtrate is put up in dark glass ampoules and stored on ice.

---

[1] Wise and Minett found filariæ, living or cretified, in the following situations : pelvis of kidney (31 times), epididymis (18 times), retroperitoneum (12 times), ilio-psoas muscle (4 times), Glisson's capsule (twice), inguinal glands (25 times), lymphatic vessels (8 times). Similar observations were made by the Editor in Fiji.

Pandit's reaction is an adhesion phenomenon. When blood containing microfilariæ is mixed with blood from a normal person and kept at room temperature for an hour or longer, the embryos become sluggish and surrounded by adherent leucocytes.

Filarial elephantiasis.—The anatomical situation of elephantiasis depends upon the distribution of the afferent lymphatic vessels. It must not be thought, however, that lymphatic elephantiasis is *solely* the product of filarial infection. The following classification of elephantiasis has been suggested by the Editor:

(*a*) Congenital or familial elephantiasis (Milroy's or Meige's disease); stenosis of main lymphatic trunks.
(*b*) Parasitic elephantiasis: *Wuchereria bancrofti*, *W. malayi*, or *Onchocerca volvulus*.
(*c*) Septic elephantiasis (*Elephantiasis nostras*—lymphatic infection by streptococci).
(*d*) Toxic elephantiasis due to absorption of irritating toxins, such as chrysarobin.
(*e*) Obstructive elephantiasis, due to tuberculous glands, carcinomatous growths, syphilis, or yaws, or to surgical removal of main lymphatic glands.
(*f*) Venous elephantiasis, secondary to venous thrombosis, such as *phlegmasia alba dolens*, or white leg.

Tesch, Brug and others have shown that elephantiasis is also produced by *Wuchereria malayi*. The difference between the two forms of lymphatic obstruction seems to lie in the predilection of this parasite for the legs rather than for the genitalia and scrotum as in *Wuchereria bancrofti* infestation.

In most cases the real origin of the obstruction lies in the fibrotic changes induced by the parasite in the lymphatic vessels and glands, leading to elephantiasis. Lymph stasis in lymphatic vessels alone does not produce elephantiasis; this has been proved by ligature of the lymphatic trunk, which results in œdema, but not in true elephantoid hypertrophy.

Anderson believed that the adult filariæ living in the lymphatic system, by the damage they produce in the intima of the vessels, so prepare the way that a streptococcal or staphylococcal infection, however mild, is able to contain a foothold and that by the changes thus produced the lymph-channels become further occluded.

O'Connor demonstrated that in filarial lymphangitis focal spots can be distinguished from which the inflammatory process commences, and that this indicates the site of a dead filaria; furthermore, that an attack of lymphangitis may be cut short by injection of sulpharsphenamine (0·2 grm. dissolved in 2 c.c. of sterile 1 per cent. novocain). This observer, with Golden and Auchincloss, found that in filariated subjects, especially in elephantiasis, calcified filariæ may be demonstrated by X-rays. The shadows range from 1 mm. in width to 2–8 mm. in length. This seems to

indicate that the infection may be quite extensive. Fifteen shadows, or groups of shadows, were detected in one elephantoid leg.

Thus can be explained the production of elephantiasis by the filaria, and the absence from the blood of the embryos of the parasite which started the disease, as they cannot pass the occluded glands. Very likely the parent worm, or worms, die at an early stage of the disease, killed by subsequent lymphangitis, or some other undetermined cause.

This anomaly is found in other conditions produced by *W. bancrofti*. In Fiji, for instance, the Editor observed that 38·2 per cent. of the cases of elephantiasis harboured microfilariæ, while the microfilaria-rate in glandular enlargement, also of filarial origin, was 34·6 per cent. On examining all those with clinical manifestations of filarial disease, it was found that 19·7 per cent. thus affected had microfilariæ in the blood, but that 44·8 per cent. of those with numerous microfilariæ showed no obvious sign of disease. As in the case of *W. malayi*, it is possible that the non-periodic *W. bancrofti* in the Pacific produces its own peculiar pathological picture. This filaria lives mostly in the lymphatic glands and produces phenomena which are connected with these structures. It has a special preference for the epitrochlear glands, and is therefore likely to produce elephantiasis of the arms. It does not produce either chyluria or lymphuria as does the periodic *W. bancrofti*.

SYMPTOMS, DIAGNOSIS, AND TREATMENT OF FILARIAL DISEASES

Enumeration of filarial diseases.—The diseases known to be produced by or associated with *W. bancrofti* are—abscess ; lymphangitis ; arthritis ; synovitis ; abscess of hip-joint ; varicose groin glands ; varicose axillary glands ; lymph scrotum ; cutaneous and deep lymphatic varix ; orchitis ; funiculitis ; hydrocele ; chyluria ; elephantiasis of the leg, scrotum, vulva, arm, mamma, and other parts ; chylous dropsy of the tunica vaginalis ; chylous ascites ; chylous diarrhœa, and probably other forms of disease depending on obstruction or varicosity of the lymphatics, or on the death or injury of the parent filariæ in a lymphatic abscess—including fatal peritonitis and secondary infections by pyogenic micro-organisms (filarial abdomen).

Abscess.—Occasionally, as already mentioned, whether in consequence of blows or other injuries, of lymphangitis, or of unknown causes, the parent filariæ die. Generally the dead body is absorbed, just as a piece of aseptic catgut would be, or becomes cretified.[1] Sometimes the dead worm acts as an irritant and causes abscess, in the contents of which fragments of the filaria may be found. Such abscesses, occurring in the limbs or scrotum, will discharge in due course, or may be opened ; if properly treated surgically, they may lead to no further trouble. Should they form in the thorax or abdomen, serious consequences and even death may ensue.

The starting-point of these abscesses is, possibly, a small hæmorrhage produced by the filaria worm which becomes secondarily infected, but

when no such occurrence takes place the defunct filaria becomes cretified. This may have to be differentiated from tropical pyomyositis. (*See* p. 667.)

---

[1] Wise and Minett found filariæ, living or cretified, in the following situations : pelvis of kidney (31 times), epididymis (18 times), retroperitoneum (12 times), ilio-psoas muscle (4 times), Glisson's capsule (twice), inguinal glands (25 times), lymphatic vessels (8 times). Similar observations were made by the Editor in Fiji.

Lymphangitis and elephantoid fever.—Lymphangitis is common in all forms of filarial disease, particularly in elephantiasis, varicose glands, and lymph scrotum. In the limbs the characteristic painful cord-like swelling of the lymphatic trunks and associated glands, and the red congested streak in the superjacent skin, are usually apparent at the commencement of the attack. The attack may continue for several days, and be accompanied by severe headache, anorexia, often vomiting and sometimes delirium. After a time tension of the inflamed integument may relieve itself by lymphous discharge from the surface. Usually, th attack ends in profuse general diaphoresis. Lymphangitis may be confined to groin glands, testis, spermatic cord (endemic funiculitis) o abdominal lymphatics. When it affects an extensive abdominal varix symptoms of peritonitis rapidly develop, and may prove fatal.

Observations by Anderson and others indicate that a streptococcu may be the initial cause of lymphangitis, but some regard it as manifestation of a reaction allergic to the toxins of *W. bancrofti.* Morales-Oter and Pomales-Lebrón showed that streptococci (*streptococcus hæmolyticu* probably play some part in recurring lymphangitis, for soon after the fir attack a high degree of antistreptococcal potency develops in the blood.

In the Pacific islands a form of filarial fever is commonly met in heavil infected districts, unassociated with lymphangitis ; this probably represen inflammation of the deep-seated lumbar lymphatics or glands.

Diagnosis.—This fever, usually termed " elephantoid fever," occurs varying intervals of weeks and months, or years, in nearly all forms elephantoid disease. Its tendency to recur, the severe rigor, and tl terminal diaphoresis, caused it to be mistaken for malaria. In Barbadc where there was until recently no malaria, it is habitually called " ague In Samoa it is known as " mumu fever " ; in Fiji as " wanganga." India, Rao and Sukhatne believed that there exists a periodicity in t incidence of lymphangitis, which is greatest during the monsoon peric July to September, when humidity is high.

Treatment.—Treatment should consist in removing any cause of irri tion, in rest, elevation of the affected part, cooling lotions or wa fomentations, mild aperients, opium or morphia to relieve pain, and, tension is great, pricking or scarifying the swollen area under suita aseptic conditions. Subsequently the parts, if their position permi should be elevated and firmly bandaged. Following upon the work the Editor, Wise and Rose, suggesting that many of the symptoms filariasis are of septic origin, Anderson obtained definite amelioration his cases in British Guiana and, in some instances, freedom from sympto for a considerable period, by the injection of staphylococcal or streptococ vaccines. Pons estimated that 40 per cent. of patients treated w streptococcal vaccines or with filtrates from cultures of these organi (which appear to be more efficacious) are benefited to a marked degree

Sulphonamides are now being employed. Recently, good results w recorded by Earle with proseptasine (sulphanilamide) in 0·5 grm. d given every four hours. Prontosil has been given with advantage, and also sulphathiazole. Should further experience bear out these claims, it would greatly strengthen the theory of secondary streptococcal infection.

Varicose groin-glands (Fig. 160).—Varicose groin-glands are frequently associated with lymph scrotum, with chylous dropsy of the tunica vaginalis, or with chyluria. Occasionally all four conditions may co-exist in the same individual.

As a rule, the patient is not aware of the existence of varicose glands until they have attained considerable dimensions. Then, a sense of tension, or an attack of lymphangitis, calls attention to the state of the groins, where certain soft swellings are discovered. These swellings may be of insignificant dimensions or they may attain the size of a fist. They may involve both, or only one groin; they may affect the inguinal glands, or the femoral glands alone, or (more usually) both sets together.

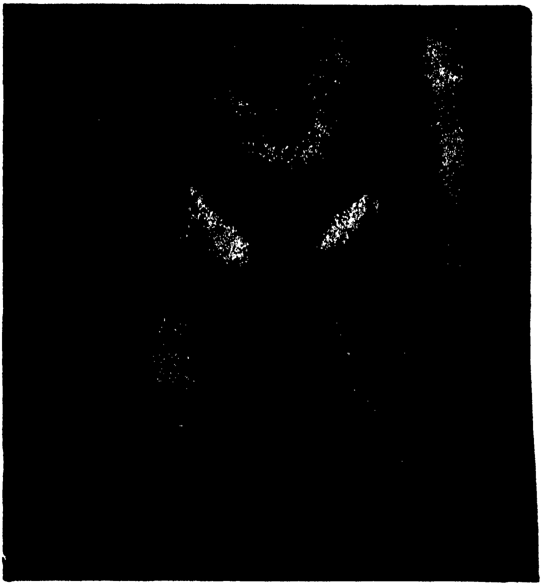


Fig. 160.—Varicose groin-glands and chylocele.

Diagnosis.—It is important to be able to diagnose these tumours from hernia, for which they are often mistaken. This can be done by observing that they are not tympanitic on percussion; that, though pressure causes them to diminish, they do so slowly; that there is no sudden dispersion on taxis, accompanied by gurgling, as in hernia; that they convey a relatively slight or no impulse on coughing; that they slowly subside when the patient lies down, and slowly return, even if pressure be applied over the saphenous or inguinal openings, on the erect posture being resumed. The cautious use of the hypodermic needle will confirm diagnosis, which may reveal microfilariæ, or actually filarial eggs, and the diagnosis is further strengthened by the co-existence of lymph scrotum chyluria, or chylous hydrocele, and microfilariæ in the blood. *Chroni swellings about the groin, cord, testis and scrotum in patients from the tropic should always be regarded as possibly of filarial origin.*

Treatment.—Unless they give rise to an incapacitating amount o discomfort, and are the seat of frequent attacks of lymphangitis, varicos groin-glands are best left alone. Excision is not always satisfactory, a it may be followed by lymphorrhagia at the seat of the wound, by excessi dilatation of some other part of the implicated lymphatic area, by chylur or by elephantiasis of one or both legs.

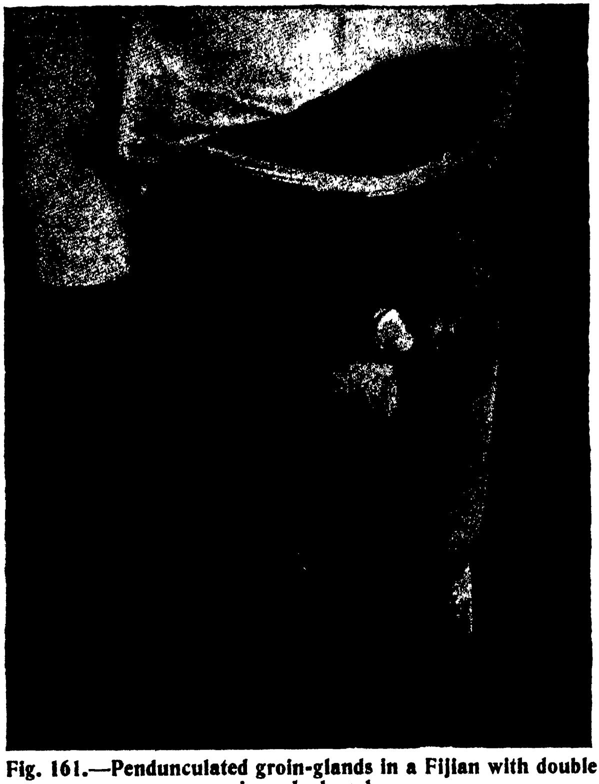


Fig. 161.—Pendunculated groin-glands in a Fijian with double varicose hydrocele.

These glands, containing adult ♂ and ♀ filariæ, were removed at operation. No microfilariæ were found in the blood. There were also masses of enlarged glands in the right groin.

Similar varicose dilatation of the axillary glands is sometimes, thou much more rarely, found. Bancroft designated varicose axillary a groin glands " helminthoma elastica."

Cutaneous and deeper lymphatic varices.—Occasionally cutane lymphatic varices are seen on the surface of the abdomen, on the le arms, and probably elsewhere. Filarial lymphangiectasis of the spermatic cord is not uncommon. The contents may be milky and chylous, or straw-coloured and lymphous, according to situation and connections.

Thickened lymphatic trunks.—After the initial swelling and inflammation of lymphangitis have subsided, a line of induration remains. On excising this thickened tissue and carefully dissecting it, minute cyst-like dilatations of the lymphatic involved were found by Maitland, Daniels, and the Editor, and in these cysts adult filariæ, sometimes dead.

Filarial glandular enlargement.—In the Pacific islands great enlargement of the lymphatic glands with fibrotic changes is by far the most frequent symptom of filarial disease. The epitrochlear gland, for instance, is often affected—in Fiji in 22 per cent. of the population.

The groin-glands are often very much enlarged, sometimes to 2 or 3 in. in diameter, and may form permanent tumours in the groin. On section they have the appearance of an unripe pear, the central portion being fibrotic, the peripheral glandular. The deep-seated glands—iliac, lumbar, mesenteric, and mediastinal—may also be enlarged. On dissection, live filariæ or their calcified remains may be demonstrated. (Fig. 161.)

Treatment. — Usually it is inadvisable to remove these glands, seeing that, as with varicose groin-glands, incurable lymphocele might result.

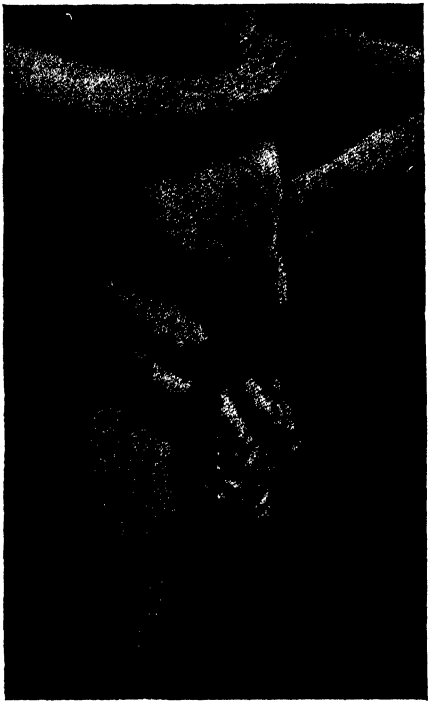


Fig. 162.—Lymph scrotum and varicose groin-glands.
(Photo: Dr. Rennie.)

Lymph scrotum (Fig. 162).—In this disease the scrotum is more or less enlarged. Though usually silky to the touch, on inspection the skin presents a few or a large number of smaller or larger lymphatic varices which, when pricked or when they rupture spontaneously, discharge large quantities of milky or sanguineous-looking or straw-coloured, rapidly-coagulating lymph or chyle. In some cases 8 or 10 oz. of this substance will escape from a puncture in the course of an hour or so; it may go on running for many hours on end, soiling the clothes and exhausting the patient. Usually, microfilariæ can be discovered in the lymph so obtained, as well as in the blood. In a large proportion of cases of lymph scrotum the inguinal and femoral glands, either on one or on both sides, are varicose.

Treatment.—Unless inflammation is frequent, or there is frequent and debilitating lymphorrhagia, or unless the disease tends to pass into true elephantiasis, lymph scrotum—kept scrupulously clean, powdered with boracic acid, suspended, and protected—had better be left alone. Should it, however, be deemed expedient to remove the diseased tissues, this can be easily done. The scrotum should be well dragged down by an assistant while the testes are pushed up out of the way of injury. A finger knife is then passed through the scrotum, and in sound tissues, just clear of the testes, the mass is excised by cutting backwards and forwards. No diseased tissues and hardly any flap should be left. Sufficient covering for the testes can be obtained by dragging on and, if necessary, dissecting up the skin of the thighs, which readily yields and affords ample covering. It is a very common but a very great mistake to remove too little. As a rule, the wound, if carefully stitched and dressed antiseptically, heals rapidly.

In consequence of this violent interference with a large varix, of which that in the scrotum is but a part, chyluria or elephantiasis of a leg may supervene. The patient should be warned of this possibility.

Chyluria.—When a lymphatic varix ruptures in the wall of the bladder, or elsewhere in the urinary tract, in the thoracic duct or in the lymphatics of the urinary system, there is an escape of the contents of the lymphatics into the urine. Chyluria is the result. If, as often happens, it contains blood, the condition is known as hæmatochyluria.

A curious fact about this form of filarial disease is that in the Pacific islands it is practically unknown, though quite common in India, China, and North Africa. It frequently appears without warning; usually, however, pain in the back and aching sensations about the pelvis and groins—probably caused by great distension of the pre-existing lymphatic varix—precede it. Retention of urine, from the presence of chylous or lymphous coagula, is sometimes the first indication of serious trouble. Whether preceded by aching, or by retention, or by other symptoms, the patient becomes suddenly aware that he is passing milky urine. Sometimes, instead of being white, the urine is pinkish, or even red; sometimes, white in the morning, it is reddish in the evening, or *vice versa*. Sometimes, while chylous at one part of the day, it is perfectly limpid at another. Great variety in this respect exists in different cases, and even in the same case from time to time, depending on temporary closure of the rupture in the lymphatic, and also on the nature of the food.[1] Chyluria is very likely to occur, either for the first time or as a relapse, in pregnancy or after childbirth.

Physical characters of chylous urine.—If chylous urine be passed into a urine-glass and allowed to stand, within a very short time, as a rule, the whole of the urine becomes coagulated. Gradually, the coagulum contracts until, at the end of some hours, a small, more or less globular clot, usually bright red or pinkish, is floating about in a milky fluid, the appearance of which is entirely due to suspended fat particles. Later, the fluid separates into three layers. On the top there is a cream-like pellicle; at the bottom, a scanty reddish sediment, sometimes including minute red clots; in the centre the mass of the urine forms a thick, intermediate stratum, milky white or reddish white, in which pipette and examined with the microscope, it is found to contain red blood-corpuscles, lymphocytes, granular fatty matter, epithelium and urinary salts, and mixed with these in a large proportion of cases, though not in all, microfilariæ. The middle layer contains much granular fatty matter; while the upper, cream-like layer consists of the same fatty material in greater abundance, the granules tending to aggregate into larger oil globules. If a little of the coagulum be teased out, pressed between two slides, and examined with the microscope, microfilariæ, more or less active, may be found entangled in the meshes of the fibrin. According to Yorke and Blacklock, the number of microfilariæ in chylous urine varies greatly within the twenty-four hours in quite an irregular manner. If ether or xylol be shaken up with the milky urine, the fat particles are dissolved out and the urine becomes clear; the fat may be recovered by decanting and evaporating the ether, which floats on the urine. Boiling the urine throws down a considerable precipitate of albumin. When the urine contains only lymph, fatty elements are absent, or are present in but very small amount. According to Young, a twenty-four-hour sample of chylous urine contains 1·8–2·6 per cent. of fat. The amount of this substance excreted is generally, though perhaps not invariably, dependent on the amount ingested.

---

[1] The sanguineous appearance so frequently seen in chylous urine and in other forms of filarial lymphorrhagia possibly depends in some instances on the formation of blood-corpuscles in lymph long retained in the varicose vessels, as a result of the normal evolution of the formed elements in that fluid. In other instances it is probably caused by rupture of small blood-vessels into the dilated lymphatics; in these cases the microfilariæ appear in the urine passed during the night-time only.

By cystoscopy the Editor has seen in the bladder the chylous vesicles which burst when fully distended, and Romiti showed by this method, as well as by ureteric catheterization, that lymphatic obstruction in a limited portion of the urinary system suffices to cause chyluria.

Although chyluria is not directly dangerous to life, yet if it is prolonged, it gives rise to pronounced anæmia, with depression of spirits and feelings of weakness and debility, and tends to incapacitate the patient for active, vigorous life.

Lymphuria.—It would be more correct to describe a certain proportion of filarial cases passing cloudy urine as "filarial lymphuria," as Low and Wise suggested. In these cases the abnormal element is lymph, and there is no trace of fat. Albumin is found in considerable quantity, and blood may be present as well. The chief cellular constituent is the lymphocyte. Low, who was able to investigate one of these cases shortly after death, found the lymphatic obstruction located in the kidney lymphatics, which was due to calcification of dead filariæ.

Treatment.—The treatment of chyluria should be conducted on the same lines as that of inaccessible varix elsewhere; that is to say, by resting and elevating the affected part, and thereby diminishing as far as possible the hydrostatic pressure in the distended vessels.

The best results are obtained by putting the patient to bed on an inclined plane with feet elevated, by restricting the amount of food and fluid, and by gentle purgation and absolute rest. Washing out the bladder with some bland substance, such as boric acid, appears to be the best form of treatment; if there is an admixture of blood, styptics may be added, as follows:

℞	Liq. adrenal. (1 in 1000) . .	℥i	(28·42 c.c.)
	Zinc. sulph.	gr.v	(0·324 grm.)
	Lot. acid. bor. ad	℥x	(284·17 c.c.)

To be used with an equal quantity of hot water.

Golden and O'Connor found improvement after X-ray treatment to the kidney region in seven cases.

by passage through a sterile Seitz asbestos filter. The filtrate is put up in dark glass ampoules and stored on ice.

Pandit's reaction is an adhesion phenomenon. When blood containing microfilariæ is mixed with blood from a normal person and kept at room temperature for an hour or longer, the embryos become sluggish and surrounded by adherent leucocytes.

Filarial elephantiasis.—The anatomical situation of elephantiasis depends upon the distribution of the afferent lymphatic vessels. It must not be thought, however, that lymphatic elephantiasis is *solely* the product of filarial infection. The following classification of elephantiasis has been suggested by the Editor:

(*a*) Congenital or familial elephantiasis (Milroy's or Meige's disease); stenosis of main lymphatic trunks.
(*b*) Parasitic elephantiasis: *Wuchereria bancrofti*, *W. malayi*, or *Onchocerca volvulus*.
(*c*) Septic elephantiasis (*Elephantiasis nostras*—lymphatic infection by streptococci).
(*d*) Toxic elephantiasis due to absorption of irritating toxins, such as chrysarobin.
(*e*) Obstructive elephantiasis, due to tuberculous glands, carcinomatous growths, syphilis, or yaws, or to surgical removal of main lymphatic glands.
(*f*) Venous elephantiasis, secondary to venous thrombosis, such as *phlegmasia alba dolens*, or white leg.

Tesch, Brug and others have shown that elephantiasis is also produced by *Wuchereria malayi*. The difference between the two forms of lymphatic obstruction seems to lie in the predilection of this parasite for the legs rather than for the genitalia and scrotum as in *Wuchereria bancrofti* infestation.

In most cases the real origin of the obstruction lies in the fibrotic changes induced by the parasite in the lymphatic vessels and glands, leading to elephantiasis. Lymph stasis in lymphatic vessels alone does not produce elephantiasis; this has been proved by ligature of the lymphatic trunk, which results in œdema, but not in true elephantoid hypertrophy.

Anderson believed that the adult filariæ living in the lymphatic system, by the damage they produce in the intima of the vessels, so prepare the way that a streptococcal or staphylococcal infection, however mild, is able to contain a foothold and that by the changes thus produced the lymph-channels become further occluded.

O'Connor demonstrated that in filarial lymphangitis focal spots can be distinguished from which the inflammatory process commences, and that this indicates the site of a dead filaria; furthermore, that an attack of lymphangitis may be cut short by injection of sulpharsphenamine (0·2 grm. dissolved in 2 c.c. of sterile 1 per cent. novocain). This observer, with Golden and Auchincloss, found that in filariated subjects, especially in elephantiasis, calcified filariæ may be demonstrated by X-rays. The shadows range from 1 mm. in width to 2–3 mm. in length. This seems to

indicate that the infection may be quite extensive. Fifteen shadows, or groups of shadows, were detected in one elephantoid leg.

Thus can be explained the production of elephantiasis by the filaria, and the absence from the blood of the embryos of the parasite which started the disease, as they cannot pass the occluded glands. Very likely the parent worm, or worms, die at an early stage of the disease, killed by subsequent lymphangitis, or some other undetermined cause.

This anomaly is found in other conditions produced by *W. bancrofti.* In Fiji, for instance, the Editor observed that 38·2 per cent. of the cases of elephantiasis harboured microfilariæ, while the microfilaria-rate in glandular enlargement, also of filarial origin, was 34·6 per cent. On examining all those with clinical manifestations of filarial disease, it was found that 19·7 per cent. thus affected had microfilariæ in the blood, but that 44·8 per cent. of those with numerous microfilariæ showed no obvious sign of disease. As in the case of *W. malayi*, it is possible that the non-periodic *W. bancrofti* in the Pacific produces its own peculiar pathological picture. This filaria lives mostly in the lymphatic glands and produces phenomena which are connected with these structures. It has a special preference for the epitrochlear glands, and is therefore likely to produce elephantiasis of the arms. It does not produce either chyluria or lymphuria as does the periodic *W. bancrofti.*

SYMPTOMS, DIAGNOSIS, AND TREATMENT OF FILARIAL DISEASES

Enumeration of filarial diseases.—The diseases known to be produced by or associated with *W. bancrofti* are—abscess: lymphangitis; arthritis; synovitis; abscess of hip-joint; varicose groin glands; varicose axillary glands; lymph scrotum; cutaneous and deep lymphatic varix; orchitis; funiculitis; hydrocele; chyluria; elephantiasis of the leg, scrotum, vulva, arm, mamma, and other parts; chylous dropsy of the tunica vaginalis; chylous ascites; chylous diarrhœa, and probably other forms of disease depending on obstruction or varicosity of the lymphatics, or on the death or injury of the parent filariæ in a lymphatic abscess—including fatal peritonitis and secondary infections by pyogenic micro-organisms (filarial abdomen).

Abscess.—Occasionally, as already mentioned, whether in consequence of blows or other injuries, of lymphangitis, or of unknown causes, the parent filariæ die. Generally the dead body is absorbed, just as a piece of aseptic catgut would be, or becomes cretified.[1] Sometimes the dead worm acts as an irritant and causes abscess, in the contents of which fragments of the filaria may be found. Such abscesses, occurring in the limbs or scrotum, will discharge in due course or may be opened; if properly treated surgically, they may lead to no further trouble. Should they form in the thorax or abdomen, serious consequences and even death may ensue.

The starting-point of these abscesses is, possibly, a small hæmorrhage produced by the filaria worm which becomes secondarily infected, but

when no such occurrence takes place the defunct filaria becomes cretified. This may have to be differentiated from tropical pyomyositis. (*See* p. 667.)

---

[1] Wise and Minett found filariæ, living or cretified, in the following situations: pelvis of kidney (31 times), epididymis (18 times), retroperitoneum (12 times), ilio-psoas muscle (4 times), Glisson's capsule (twice), inguinal glands (25 times), lymphatic vessels (8 times). Similar observations were made by the Editor in Fiji.

Lymphangitis and elephantoid fever.—Lymphangitis is common in all forms of filarial disease, particularly in elephantiasis, varicose glands, and lymph scrotum. In the limbs the characteristic painful cord-like swelling of the lymphatic trunks and associated glands, and the red congested streak in the superjacent skin, are usually apparent at the commencement of the attack. The attack may continue for several days, and be accompanied by severe headache, anorexia, often vomiting, and sometimes delirium. After a time tension of the inflamed integuments may relieve itself by lymphous discharge from the surface. Usually, the attack ends in profuse general diaphoresis. Lymphangitis may be confined to groin glands, testis, spermatic cord (endemic funiculitis) or abdominal lymphatics. When it affects an extensive abdominal varix, symptoms of peritonitis rapidly develop, and may prove fatal.

Observations by Anderson and others indicate that a streptococcus may be the initial cause of lymphangitis, but some regard it as manifestation of a reaction allergic to the toxins of *W. bancrofti*. Morales-Otero and Pomales-Lebrón showed that streptococci (*streptococcus hæmolyticus*) probably play some part in recurring lymphangitis, for soon after the first attack a high degree of antistreptococcal potency develops in the blood.

In the Pacific islands a form of filarial fever is commonly met in heavily-infected districts, unassociated with lymphangitis ; this probably represents inflammation of the deep-seated lumbar lymphatics or glands.

Diagnosis.—This fever, usually termed " elephantoid fever," occurs at varying intervals of weeks and months, or years, in nearly all forms of elephantoid disease. Its tendency to recur, the severe rigor, and the terminal diaphoresis, caused it to be mistaken for malaria. In Barbados, where there was until recently no malaria, it is habitually called " ague." In Samoa it is known as " mumu fever " ; in Fiji as " wanganga." In India, Rao and Sukhatne believed that there exists a periodicity in the incidence of lymphangitis, which is greatest during the monsoon period, July to September, when humidity is high.

Treatment.—Treatment should consist in removing any cause of irritation, in rest, elevation of the affected part, cooling lotions or warm fomentations, mild aperients, opium or morphia to relieve pain, and, if tension is great, pricking or scarifying the swollen area under suitable aseptic conditions. Subsequently the parts, if their position permits, should be elevated and firmly bandaged. Following upon the work of the Editor, Wise and Rose, suggesting that many of the symptoms of filariasis are of septic origin, Anderson obtained definite amelioration in his cases in British Guiana and, in some instances, freedom from symptoms for a considerable period, by the injection of staphylococcal or streptococcal vaccines. Pons estimated that 40 per cent. of patients treated with streptococcal vaccines or with filtrates from cultures of these organisms (which appear to be more efficacious) are benefited to a marked degree.

Sulphonamides are now being employed. Recently, good results were recorded by Earle with proseptasine (sulphanilamide) in 0·5 grm. doses given every four hours. Prontosil has been given with advantage, and also sulphathiazole. Should further experience bear out these claims, it would greatly strengthen the theory of secondary streptococcal infection.

Varicose groin-glands (Fig. 160).—Varicose groin-glands are frequently associated with lymph scrotum, with chylous dropsy of the tunica vaginalis, or with chyluria. Occasionally all four conditions may co-exist in the same individual.

As a rule, the patient is not aware of the existence of varicose glands until they have attained considerable dimensions. Then, a sense of tension, or an attack of lymphangitis, calls attention to the state of the groins, where certain soft swellings are discovered. These swellings may be of insignificant dimensions or they may attain the size of a fist. They may involve both, or only one groin ; they may affect the inguinal glands, or the femoral glands alone, or (more usually) both sets together.

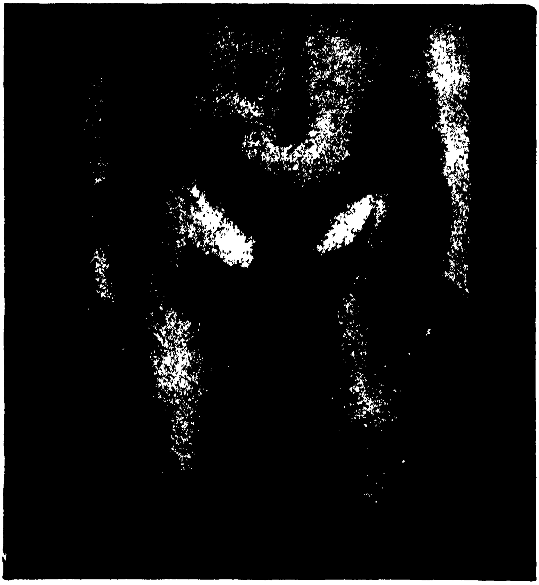


Fig. 160.—Varicose groin-glands and chylocele.

Diagnosis.—It is important to be able to diagnose these tumours from hernia, for which they are often mistaken. This can be done by observing that they are not tympanitic on percussion ; that, though pressure causes them to diminish, they do so slowly ; that there is no sudden dispersion on taxis, accompanied by gurgling, as in hernia ; that they convey a relatively slight or no impulse on coughing ; that they slowly subside when the patient lies down, and slowly return, even if pressure be applied over the saphenous or inguinal openings, on the erect posture being resumed. The cautious use of the hypodermic needle will confirm diagnosis, which may reveal microfilariæ, or actually filarial eggs, and the diagnosis is further strengthened by the co-existence of lymph scrotum, chyluria, or chylous hydrocele, and microfilariæ in the blood. *Chronic swellings about the groin, cord, testis and scrotum in patients from the tropics should always be regarded as possibly of filarial origin.*

Treatment.—Unless they give rise to an incapacitating amount of discomfort, and are the seat of frequent attacks of lymphangitis, varicose groin-glands are best left alone. Excision is not always satisfactory, as it may be followed by lymphorrhagia at the seat of the wound, by excessive dilatation of some other part of the implicated lymphatic area, by chyluria, or by elephantiasis of one or both legs.

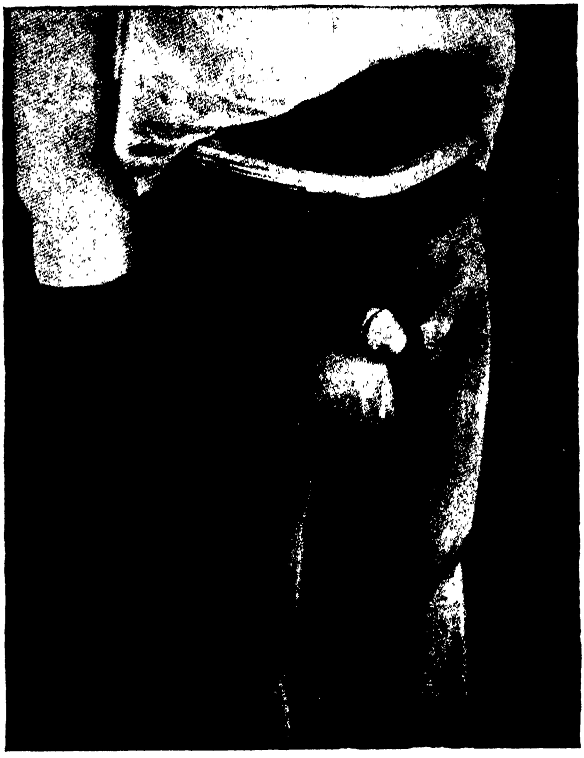


Fig. 161.—Penduncculated groin-glands in a Fijian with double varicose hydrocele.

These glands, containing adult ♂ and ♀ filariæ, were removed at operation. No microfilariæ were found in the blood. There were also masses of enlarged glands in the right groin.

Similar varicose dilatation of the axillary glands is sometimes, though much more rarely, found. Bancroft designated varicose axillary and groin glands "helminthoma elastica."

Cutaneous and deeper lymphatic varices.—Occasionally cutaneous lymphatic varices are seen on the surface of the abdomen, on the legs, arms, and probably elsewhere. Filarial lymphangiectasis of the spermatic cord is not uncommon. The contents may be milky and chylous, or straw-coloured and lymphous, according to situation and connections.

Thickened lymphatic trunks.—After the initial swelling and inflammation of lymphangitis have subsided, a line of induration remains. On excising this thickened tissue and carefully dissecting it, minute cyst-like dilatations of the lymphatic involved were found by Maitland, Daniels, and the Editor, and in these cysts adult filariæ, sometimes dead.

Filarial glandular enlargement.—In the Pacific islands great enlargement of the lymphatic glands with fibrotic changes is by far the most frequent symptom of filarial disease. The epitrochlear gland, for instance, is often affected—in Fiji in 22 per cent. of the population.

The groin-glands are often very much enlarged, sometimes to 2 or 3 in. in diameter, and may form permanent tumours in the groin. On section they have the appearance of an unripe pear, the central portion being fibrotic, the peripheral glandular. The deep-seated glands—iliac, lumbar, mesenteric, and mediastinal—may also be enlarged. On dissection, live filariæ or their calcified remains may be demonstrated. (Fig. 161.)

Treatment. — Usually it is inadvisable to remove these glands, seeing that, as with varicose groin-glands, incurable lymphocele might result.

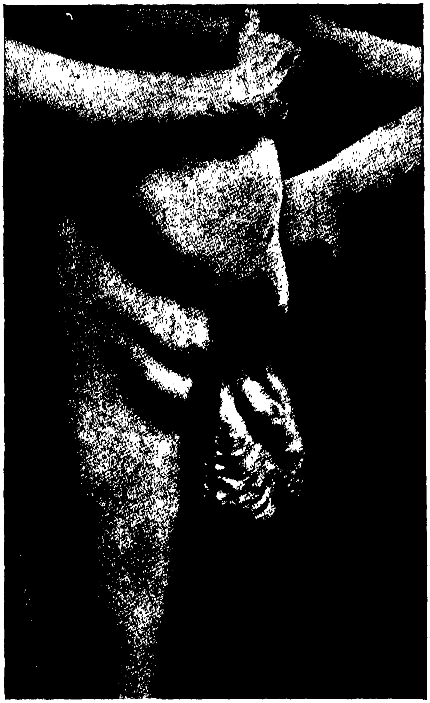


Fig. 162.—Lymph scrotum and varicose groin-glands.
(*Photo: Dr. Rennie.*)

Lymph scrotum (Fig. 162).—In this disease the scrotum is more or less enlarged. Though usually silky to the touch, on inspection the skin presents a few or a large number of smaller or larger lymphatic varices which, when pricked or when they rupture spontaneously, discharge large quantities of milky or sanguineous-looking or straw-coloured, rapidly-coagulating lymph or chyle. In some cases 8 or 10 oz. of this substance will escape from a puncture in the course of an hour or so ; it may go on running for many hours on end, soiling the clothes and exhausting the patient. Usually, microfilariæ can be discovered in the lymph so obtained, as well as in the blood. In a large proportion of cases of lymph scrotum the inguinal and femoral glands, either on one or on both sides, are varicose.

Treatment.—Unless inflammation is frequent, or there is frequent and debilitating lymphorrhagia, or unless the disease tends to pass into true elephantiasis, lymph scrotum—kept scrupulously clean, powdered with boracic acid, suspended, and protected—had better be left alone. Should it, however, be deemed expedient to remove the diseased tissues, this can be easily done. The scrotum should be well dragged down by an assistant while the testes are pushed up out of the way of injury. A finger knife is then passed through the scrotum, and in sound tissues, just clear of the testes, the mass is excised by cutting backwards and forwards. No diseased tissues and hardly any flap should be left. Sufficient covering for the testes can be obtained by dragging on and, if necessary, dissecting up the skin of the thighs, which readily yields and affords ample covering. It is a very common but a very great mistake to remove too little. As a rule, the wound, if carefully stitched and dressed antiseptically, heals rapidly.

In consequence of this violent interference with a large varix, of which that in the scrotum is but a part, chyluria or elephantiasis of a leg may supervene. The patient should be warned of this possibility.

Chyluria.—When a lymphatic varix ruptures in the wall of the bladder, or elsewhere in the urinary tract, in the thoracic duct or in the lymphatics of the urinary system, there is an escape of the contents of the lymphatics into the urine. Chyluria is the result. If, as often happens, it contains blood, the condition is known as hæmatochyluria.

A curious fact about this form of filarial disease is that in the Pacific islands it is practically unknown, though quite common in India, China, and North Africa. It frequently appears without warning: usually, however, pain in the back and aching sensations about the pelvis and groins—probably caused by great distension of the pre-existing lymphatic varix—precede it. Retention of urine, from the presence of chylous or lymphous coagula, is sometimes the first indication of serious trouble. Whether preceded by aching, or by retention, or by other symptoms, the patient becomes suddenly aware that he is passing milky urine. Sometimes, instead of being white, the urine is pinkish, or even red; sometimes, white in the morning, it is reddish in the evening, or *vice versa*. Sometimes, while chylous at one part of the day, it is perfectly limpid at another. Great variety in this respect exists in different cases, and even in the same case from time to time, depending on temporary closure of the rupture in the lymphatic, and also on the nature of the food.[1] Chyluria is very likely to occur, either for the first time or as a relapse, in pregnancy or after childbirth.

Physical characters of chylous urine.—If chylous urine be passed into a urine-glass and allowed to stand, within a very short time, as a rule, the whole of the urine becomes coagulated. Gradually, the coagulum contracts until, at the end of some hours, a small, more or less globular clot, usually bright red or pinkish, is floating about in a milky fluid, the appearance of which is entirely due to suspended fat particles. Later, the fluid separates into three layers. On the top there is a cream-like pellicle; at the bottom, a scanty reddish sediment, sometimes including minute red clots; in the centre the mass of the urine forms a thick, intermediate stratum, milky white or reddish white, in which floats the contracted coagulum. If a little of the sediment be taken up with a pipette and examined with the microscope, it is found to contain red blood-corpuscles, lymphocytes, granular fatty matter, epithelium and urinary salts, and mixed with these in a large proportion of cases, though not in all, microfilariæ. The middle layer contains much granular fatty matter ; while the upper, cream-like layer consists of the same fatty material in greater abundance, the granules tending to aggregate into larger oil globules. If a little of the coagulum be teased out, pressed between two slides, and examined with the microscope, microfilariæ, more or less active, may be found entangled in the meshes of the fibrin. According to Yorke and Blacklock, the number of microfilariæ in chylous urine varies greatly within the twenty-four hours in quite an irregular manner. If ether or xylol be shaken up with the milky urine, the fat particles are dissolved out and the urine becomes clear ; the fat may, be recovered by decanting and evaporating the ether, which floats on the urine. Boiling the urine throws down a considerable precipitate of albumin. When the urine contains only lymph, fatty elements are absent, or are present in but very small amount. According to Young, a twenty-four-hour sample of chylous urine contains 1·8–2·6 per cent. of fat. The amount of this substance excreted is generally, though perhaps not invariably, dependent on the amount ingested.

---

[1] The sanguineous appearance so frequently seen in chylous urine and in other forms of filarial lymphorrhagia possibly depends in some instances on the formation of blood-corpuscles in lymph long retained in the varicose vessels, as a result of the normal evolution of the formed elements in that fluid. In other instances it is probably caused by rupture of small blood-vessels into the dilated lymphatics; in these cases the microfilariæ appear in the urine passed during the night-time only.

By cystoscopy the Editor has seen in the bladder the chylous vesicles which burst when fully distended, and Romiti showed by this method, as well as by ureteric catheterization, that lymphatic obstruction in a limited portion of the urinary system suffices to cause chyluria.

Although chyluria is not directly dangerous to life, yet if it is prolonged, it gives rise to pronounced anæmia, with depression of spirits and feelings of weakness and debility, and tends to incapacitate the patient for active, vigorous life.

Lymphuria.—It would be more correct to describe a certain proportion of filarial cases passing cloudy urine as " filarial lymphuria," as Low and Wise suggested. In these cases the abnormal element is lymph, and there is no trace of fat. Albumin is found in considerable quantity, and blood may be present as well. The chief cellular constituent is the lymphocyte. Low, who was able to investigate one of these cases shortly after death, found the lymphatic obstruction located in the kidney lymphatics, which was due to calcification of dead filariæ.

Treatment.—The treatment of chyluria should be conducted on the same lines as that of inaccessible varix elsewhere ; that is to say, by resting and elevating the affected part, and thereby diminishing as far as possible the hydrostatic pressure in the distended vessels.

The best results are obtained by putting the patient to bed on an inclined plane with feet elevated, by restricting the amount of food and fluid, and by gentle purgation and absolute rest. Washing out the bladder with some bland substance, such as boric acid, appears to be the best form of treatment ; if there is an admixture of blood, styptics may be added, as follows :

℞	Liq. adrenal. (1 in 1000) . .	℥i	(28·42 c.c.)
	Zinc. sulph.	gr.v	(0·324 grm.)
	Lot. acid. bor. ad . . .	℥x	(284·17 c.c.)

To be used with an equal quantity of hot water.

Golden and O'Connor found improvement after X-ray treatment to the kidney region in seven cases.

Chylous dropsy of the tunica vaginalis, and of the peritoneum; chylous diarrhœa.—Chylous dropsy of the tunica vaginalis is not unusual in the tropics. A fluctuating swelling which does not transmit light, and which is associated possibly with lymph scrotum, with varicose groin-glands, with chyluria, or with micro-filariæ in the blood, would suggest this condition.

Treatment.—These chyloceles may be treated as ordinary hydroceles, either by aseptic incision or by injection. As a rule, the chylous fluid rapidly coagulates when withdrawn, but occasionally it does not, or it may be prevented by drawing the fluid off into a solution of potassium citrate.

If a minute portion of absorbent cotton is dipped into the receptacle, it will slowly fall to the bottom of the fluid. If the cotton is now picked up and placed under a low-power microscope, it will be found that every fibre is beset with multitudes of wriggling microfilariæ entangled by their sheaths, the preparation suggesting the snake-beset Gorgon head.

Filarial orchitis with effusion into the tunica vaginalis, according to Maitland, is best treated by incision of the tunica vaginalis, turning out any clot that may be found in the sac, and stuffing the latter with iodoform gauze.

Chylous dropsy of the peritoneum and chylous diarrhœa of filarial origin are very rare.

Filarial orchitis, endemic funiculitis, and hydrocele.—The fever attending filarial orchitis—which is usually associated with lymphangitis of the spermatic cord—has been described as "endemic funiculitis," but it is undoubtedly of filarial origin. It may be attended with inflammation of the scrotum, and, like ordinary elephantoid fever, resemble very closely a malarial attack. In these cases the Editor originally demonstrated large numbers of microfilariæ in the tunica vaginalis at the commencement of each attack. The aspirated fluid is cloudy, contains a number of polymorphonuclear cells, and occasionally erythrocytes, with microfilariæ. The epididymis is enlarged and nodular. In sections, dead and calcified filariæ blocking the vasa efferentia cause extensive fibrotic changes, and it is possible that sterility may be a direct result of this infestation.

The primary lesion is a sterile inflammatory reaction about a dead worm in a lymphatic vessel. With the vessel occluded, an obliterative lymphangitis results, which in turn causes dilatation, hypertrophy and varicosity with peripheral lymph stasis. The lymphatics of the testis are specially vulnerable to such lesions as they are long, without collaterals, and drain against gravity. Lymph stasis in the testicle is shown by definite clinical signs in the cord, epididymis and testis.

Recurrent attacks of filarial orchitis lead sooner or later to *hydrocele*. This condition very commonly accompanies elephantiasis of the scrotum, especially among Polynesians. The walls of the sac are thickened and contain calcified remains of adult filariæ; the hydrocele fluid is clear, straw-coloured, and usually contains microfilariæ, though it does not seem to be a medium particularly favourable to them. Filarial infiltrations of the cords vary in size, form, and number. There may be one single nodule as small as a pea, or a number may be strung to thickened lymphatic vessels. Sometimes lymphatic obstruction affects the vessels so as to cause lymphangiectasis and lymphatic varicoceles ; it may, however, cause cystic dilatation, or "lymphocele." The spermatic veins are often the seat of chronic thrombo-phlebitis.

Treatment.—The living membranes of the sac can be obliterated by injection or open operation. Injection treatment is suitable for the small, flaccid, thin-walled sacs, but operation is better for the others.

These conditions can best be treated by surgical means, though Earle claims that sulphapyridine in doses of 4 grm. daily cuts short attacks of orchitis and funiculitis.

Differential diagnosis has to be made from encysted hydrocele, lipoma, spermatocele, vaginal hydrocele, syphilitic orchitis, gonorrhœal epididymitis, strangulated hernia, and suppuration of the spermatic cord.

Septicæmia.—Fatal septicæmia due to *Streptococcus hæmolyticus* is not infrequent in subjects infected with *W. bancrofti.* Apparently the parent worm in the lymphatic system damages the lining of the vessels, and thus prepares the ground for pyogenic organisms which invade the lymph-stream. In damaged lymphatic tissue streptococci find a favourable medium, and enter the blood-stream, and septicæmia results.

Filarial synovitis.—Acute synovitis of the knee-joint is one of the filarial diseases, and its concurrence with filarial invasion is too common to be accidental ; fibrotic ankylosis often results. Where the hip-joint is affected, removal of the inflamed iliac glands draining the area sometimes relieves the condition.

In severe cases synovitis may proceed to pus-formation, often with a fatal result. Surgical intervention is therefore indicated.

ELEPHANTIASIS

In certain districts in Cochin about 5 per cent. of the population, in Samoa about every second individual, and in Huahine seven-tenths of the adult male population, are affected by this disease. In the Ellice Islands, out of a total population of 3,434, 90 per cent. are affected. In many other tropical and subtropical countries elephantiasis, if not so common as in those mentioned, is, nevertheless, very prevalent.

The pathology of the disease is considered on p. 715.

Parts affected.—In 95 per cent. of the cases the lower extremities—either one or both—alone, or in combination with the scrotum or arms, are the seat of the disease. The foot and ankle only, or the foot and leg, or the foot, leg, and thigh may each or all be involved. The arms are more rarely attacked, though in Fiji this is comparatively common ; out of 47 cases the arms alone were affected in 10, arms and legs in 6 cases. Still more rarely involved are the mammæ, vulva and circumscribed portions of the integuments of the limbs or trunk.

In any of these situations, the disease commences with a rapidly evolved lymphangitis, dermatitis and cellulitis, accompanied by elephantoid fever. O'Connor demonstrated that the attacks arise from painful areas known as "focal spots," and in a large proportion of cases it has been possible to demonstrate dead and calcifying filariæ by X-ray examination.

The lymphatic glands draining the affected area are generally enlarged. There is no distinct line of demarcation between healthy and diseased skin. The implicated integuments are hard, dense, pit but slightly, if at all, on pressure, and cannot be pinched up or freely glided over the deeper parts.

On cutting into the swelling, the derma is found to be dense, fibrous and enormously hypertropied. The subjacent connective tissue is increased in bulk, having, especially in the scrotum, a yellowish, blubbery appearance from lymphous infiltration. A large quantity of fluid wells out on division of such tissues.

Elephantiasis of the legs. (Fig. 163).—Elephantiasis of the lower extremities is usually, though by no means always, confined to below the knee. The swelling may attain enormous dimensions and involve the entire extremity, the leg or legs attaining a circumference, in aggravated cases, of several feet.

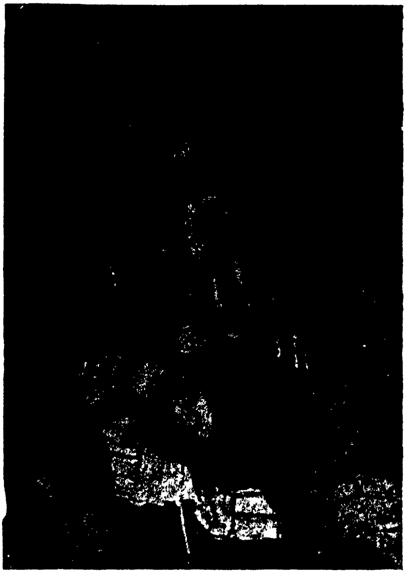


Fig. 163.—Elephantiasis of legs ; scrotum and right arm also affected. (*Photograph : Dr. Turner, Samoa.*)

Treatment.—Golden and O'Connor (1934) reported on irradiation by X-rays of lymphangitis and adenitis. At first, merely focal spots were so treated, but later the entire leg. Out of fifteen cases four had no further attacks. The patient should be encouraged to persevere with elastic bandaging, massage, and elevation of the limb. Swellings in the early stages may to some extent be controlled by elastic bandages or stockings. The latter, which should be made to fit the legs accurately, should be of some porous elastic and washable material, such as stockinette. Such a stocking (Fig. 164A) should embrace the dorsum of the foot and should accurately fit the leg to reach above the knee. Difficulty is generally experienced with the upper margin, which extends to the thigh, as it is apt to constrict or nip the limb at this point. To obviate the pressure and discomfort of tight-fitting stockings, and to accommodate the fluctuations in the size of the limb which necessarily take place, these stockings may be made to lace up at the sides (Fig. 164B). A spiral elastic stocking, made by Down Bros. on Dickson Wright's model, which can be accurately fitted to the leg and which is comfortable, airy and effective, can be recommended. The technique varies according to whether the leg is cylindrical, œdematous or lobulated. In the œdematous form bandaging methods should be employed. Knott is an advocate of prolonged and firm bandaging, which effects a gradual removal of the lymphœdema, during which time the patient obtains symptomatic relief and avoids further recurrent attacks of lymphangitis ; the bandages should not be removed when an attack of lymphangitis is imminent, but the foot of the bed should be elevated. A " bandage boot " is used, consisting of a 6-inch bandage of heavy Turkish towelling, which covers the limb from behind the heads of the metatarsals to the heads of the tibia and fibula, cemented to a covering crêpe bandage by dextrin-syrup applied along the tibia, the whole being supported by narrow lateral strips.

Operative measures.—Sometimes in advanced cases good results follow excision of redundant masses of skin. A curved incision should be made from the head of the tibia to the ankle joint ; two further incisions at upper and lower ends make a Y shaped cut. The skin is separated on both sides laterally as far as possible. The elephantoid tissues thus exposed are now incised along the whole margin as far as the periosteum and a similar incision is made parallel to this down to the muscle fascia. This separation is repeated in ring-like strips down the leg until none of the proliferated tissue remains except part of it behind the calf.

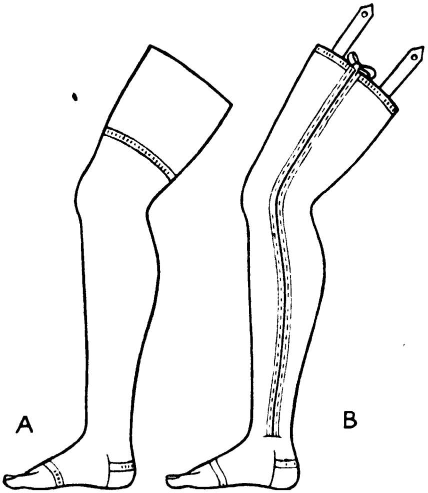


Fig. 164.—A, Plain web-elastic stocking, with foot-piece, for slight degrees of elephantiasis of leg. B, Laced form of elastic stocking, with suspenders, adjustable so as to avoid pinching. (*A, James Woolley & Sons, Manchester ; B, Hospitals & General Contract Co.*)

Junge's methods are as follows :—To restore the flow of lymph, about twenty-five windows are cut in the muscle fasciæ over the whole of the leg, each bigger than a postage stamp, but none is cut over the tibia. Into each of these windows a double silk thread is inserted by passing the needle deep through the muscle. The hanging ends are arranged like candle-wicks to suck out lymph over the widest possible area of the leg. The skin flaps are then replaced.

Various other operative measures have been proposed, though none is entirely satisfactory. *Lanz's operation* aims at deep lymphatic drainage. A longitudinal incision is made through the fascia lata down to the femur, the periosteum of which is stripped and the bone trephined in several places ; strips of fascia are then inserted into the openings thus made.

Kondoleon's operation consists also in free incision of the fascia lata and removal of large sections of the aponeurosis, which assists in the anastomosis of lymph channels and veins.

Auchincloss's operation is intended to lighten elephantoid legs, and also to remove those tender focal spots whence the inflammatory lesions of filarial fever arise and to excise calcified worms. It consists of two incisions marking out a vertical strip of skin. From its ends V-shaped incisions are made diverging upwards at the upper end and downwards at the lower. An almost dangerously wide amount of skin is undermined, with considerable care, just deep to the corium.

Medical treatment.—Bowesman has advocated a method of treatment of filarial elephantiasis by intra-arterial injection of glycerine. This depends upon the inherent attraction of glycerine for water so that, when placed in contact with living tissues, it causes a movement of the fluid from the tissue spaces towards the vessels or the region in which the glycerine is placed. Injections of 10 per cent. sterile glycerine in water are given at intervals not less than one week apart, into the femoral artery, the optimum dose being 2–3 c.c. of a 10 per cent. solution. In making the injection the needle is introduced into the artery and then the syringe containing the solution is attached. No pain or discomfort is noticed if the injection is made slowly. The effect of intravenous medication is not so marked as intra-arterial. The decrease in size of the limb appears to be fairly permanent.

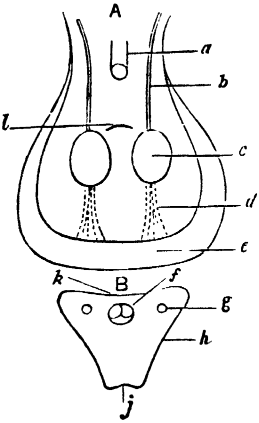


Fig. 165.—Diagram of anatomy of elephantiasis of scrotum. (For references, *see* text.)

Elephantiasis of the scrotum.—Elephantiasis of the scrotum or "scrotal tumour" as it is sometimes called, may attain an enormous size: 10, 15, 20 lb. are common weights for these tumours, and 40 or 50 lb. is by no means uncommon. The largest recorded was 224 lb.

Anatomical characters.—These tumours consist of two portions (Fig. 165): first, a dense rind of hypertrophied skin (A, *e*), thickest towards the lower part and gradually thinning out as it merges above into the sound skin of the pubes, perineum and thighs; secondly, enclosed in this rind, a mass of lax, blubbery, dropsical, areolar tissue in which testes, cords and penis are embedded. The shape of the tumour is more or less pyriform. The upper part, or neck, on transverse section (B) is triangular, the base (B, *k*) of the triangle being in front, the apex (B, *j*)—usually somewhat bifid from dragging on the gluteal folds—towards the anus, the sides (B, *h*) towards the thighs. In the latter situation the skin, though usually more or less diseased, is, from pressure, softer and thinner than elsewhere, tempting the surgeon to utilize it for the formation of flaps—not always a wise proceeding. The penis (A, *a*, B, *f*) always lies in the upper and fore part of the neck of the mass; it is firmly attached to the pubes by the suspensory ligament. The sheath of the penis is sometimes especially hypertrophied, in some cases standing out as a sort of twisted ram's-horn-like projection on the anterior surface of the tumour; this, however, is unusual. Generally the sheath of the penis is incorporated in the scrotal mass, the prepuce being dragged on and inverted so as to form a long channel leading to the glans penis and opening (A, *l*) half-way down, or even lower, on the face of the tumour. The testes (A, *c*), buried in the central blubbery tissue, usually lie towards the back of the tumour, one on each side—in large tumours generally nearer the lower than the upper part. They are more or less firmly attached to the under-part of the scrotum by the hypertrophied remains of the gubernaculum testis (A, *d*)—a feature to be specially borne in mind by the surgeon. As a rule, both testes carry large hydroceles with thickened tunicæ vaginales. The spermatic cords also (A, *b* ; B, *g*) are thickened and greatly elongated.

The arteries which supply these enormous growths are of considerable size ; the veins, too, are very large and, as they permit regurgitation of blood from the trunk, are apt to bleed freely.

Treatment before operation.—If the tumour is of considerable size the patient should keep his bed for at least a week before operation, the mass being suspended so as to drain it of fluid and blood. It is thus rendered lax, and the operator can ascertain by palpation the position of the testes and of any hernia—a not very unusual complication. The possibility of undescended testes should not be overlooked. The choice of anæsthetic is important : it should be spinal when possible, reinforced with gas and oxygen. The patient should not be kept long in bed before the operation, for when the mass is supported, the fluid drains upwards and invades the tissues to be used for flaps, and the palpable edge of the elephantoid skin is obscured.

Operation.—The patient should be placed in the lithotomy position. The scrotum should be drawn down as far as possible and elastic webbing applied over the mass so as to expel the blood ; a stout rubber cord is wound round the neck of the tumour, over the pelvis, and firmly secured. A vertical incision is made, commencing in the middle of the symphysis pubis and extending as far as the aperture leading to the penis. The penis is exposed, separated and the penal artery ligatured. It should be borne in mind that the prepuce and skin of the sheath of the penis have been pulled down over the glans, and form a skin-lined tube from the gland to an opening on the front of the tumour, and, while the skin of the prepuce and the sheath and even the frænum may be elephantoid, the skin of the glans is normal. At this point, a sound is passed, and left in to prevent subsequent injury to the urethra. The vertical incision is now continued round the scrotum right round to the back of the perineum, and the scrotum is thus divided into two halves. The testicles and cords are now separated from the blubbery mass, the hypertrophied gubernacula being divided, surrounded with gauze and placed on one side. At the base of each half of the scrotum clamps are fixed, care being taken that these clamps are well to the proximal side of all diseased tissue. Each half of the scrotum is then cut away, distal to the clamps, and through healthy tissue. Every visible blood-vessel is secured and tied and the clamps very gradually loosened. The skin in the upper and inner aspects of the thigh is undermined as much as necessary and brought together over the testicles. Thiersch skin-grafts may be applied to the penis, and give good cosmetic and functional results, and, if done at the time of the operation, will take in 100 per cent. of cases. It is a good procedure to tie in a catheter until healing has taken place.

Complications which may ensue are severe hæmorrhage, and injury to spermatic cords, urethra or rectum. Postoperative retention of urine is often very troublesome. Stricture of the urethra and the supervention of elephantiasis of a previously unaffected leg have also been recorded.

The mortality from these formidable-looking operations, if they are carefully done, is small, and need not exceed 5 per cent.

Knott insisted that the most important factor is the position of the patient on the operating table. If the patient is placed on a horizontal table with his legs over the sides supported by chairs, the mass can be rolled to the opposite side, and this does away with the need for a rubber tourniquet.

Early cases of elephantiasis of the scrotum, still subject to attacks of fever with lymphangitis and cellulitis which involves the skin of the penis and scrotum, require to be handled in a different manner. In these cases enough skin should be saved to cover the testes, and the more skin taken, the less likelihood there is of a recurrence. Modern surgeons are concerned with restoration of the penis. Some take skin from the mons veneris to cover it, others from the sides of the scrotum, but this is often diseased. The scrotal suture should be as far as possible from the anus. The suture takes the form of a double cross, and a glass or rubber drain is inserted.

Elephantiasis of the arms.—This is comparatively rare. Allowing for the gravitation differences between the upper and lower extremities, the symptoms and pathology of elephantiasis of the arms are the same as those of elephantiasis of the legs. Beyond the judicious employment of massage and elastic bandaging, little can be done in treatment. (Fig. 166.)

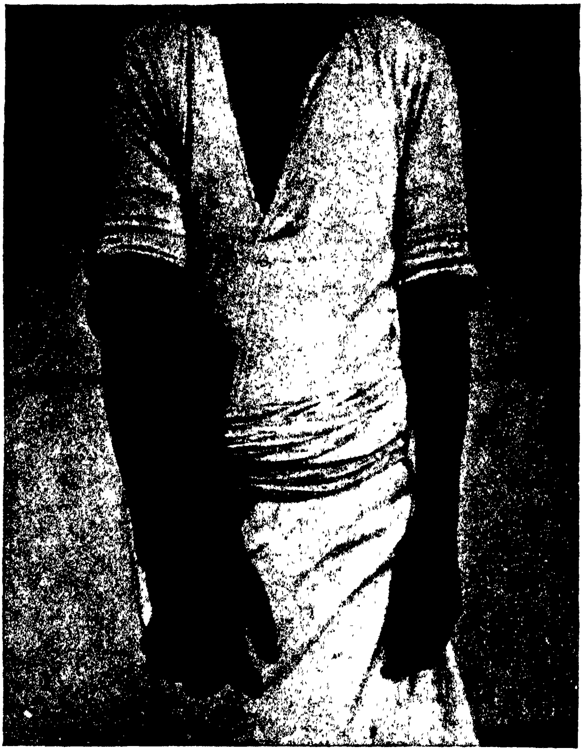


Fig. 166.—Elephantiasis of right arm and hand in a Fijian.

Elephantiasis of the vulva and mammæ.—Elephantiasis of the vulva (Fig. 167) and mammæ (Fig. 168) is still rarer. Where growth has become inconveniently large, the diseased tissues should be removed.

Instances are on record in which the integuments of the mammæ have become so thickened, heavy, and elongated that the organ has descended to the pubes, and even to the knees. One such tumour weighed 21 lb. after removal. Tumours of the labia or of the clitoris, similarly, may attain a great size—8 or 10 lb., or even more.

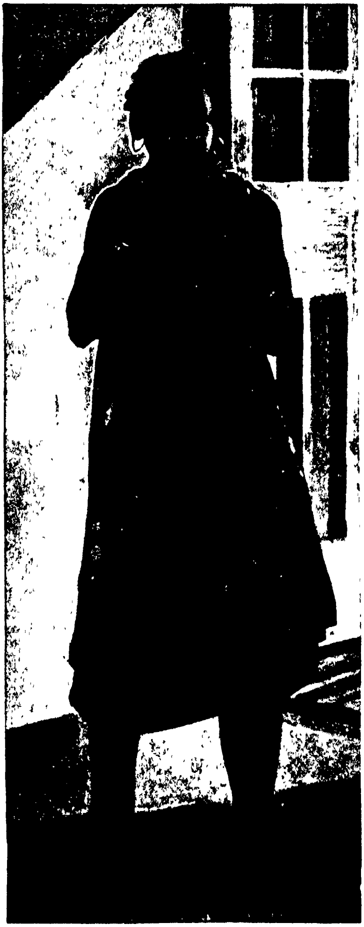


Fig. 167.—Elephantiasis of vulva.
(*Photograph : Dr. Walter H. B. Macdonald.*)

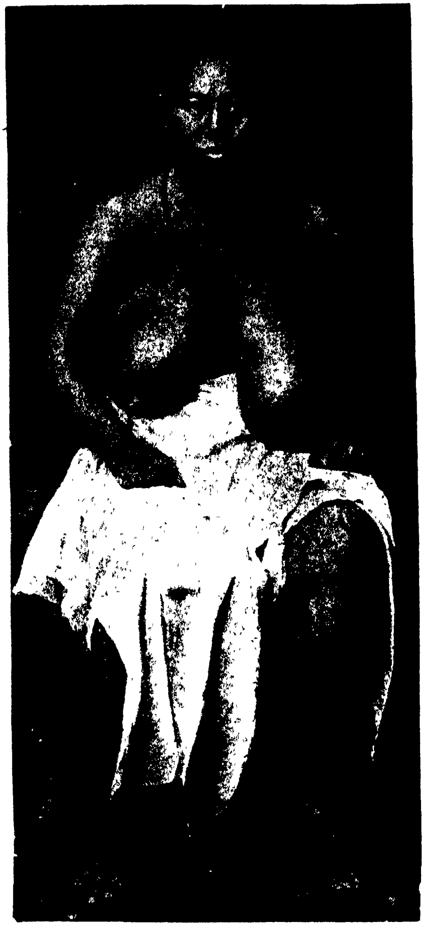


Fig. 168.—Elephantiasis of mammæ ; left leg and foot also affected.
(*Photograph : Dr. Davies, Samoa.*)

Elephantiasis of limited skin areas.—Corney stated that pedunculated elephantoid tumours, springing from the groin or from the anterior surface of the thigh, were not uncommon in Fiji. One such tumour which he removed weighed 20 lb. Daniels saw, both in Fiji and in Demerara, several cases of this description.

Filariasis and elephantiasis due to Wuchereria malayi.—It is claimed that the disease produced by this species differs in some respects from that produced by *Wuchereria bancrofti,* a fact that was recognized by Poynton and Hodgkin. *W. malayi* is endemic in Malaya, Southern India and Ceylon, in the low-lying riverine areas, where the rivers run into the sea. The microfilaria-rate in the natives living in the vicinity of swamps is 9·3 per cent., which is about the same as the elephantiasis rate ; as with *W. bancrofti,* the liability to infection increases with age.

Adenitis is the earliest detectable lesion ; inflammation of the groin-glands is frequently seen in children. Lymphangitis is also a familiar phenomenon and has a definite periodic character which is regarded (possibly correctly) as negativing its streptococcal origin. Elephantiasis due to *Wuchereria malayi* is low-grade, invariably confined to the legs, and is usually unilateral. There appears to be great variability in the rate at which elephantoid lesions are produced. In highly infected areas it is seen in comparatively young people, especially in males, though it is typically a disease of adult life. Microfilariæ are, as a rule, found only in 5 per cent. of cases.

Medicinal treatment of filariasis.—At present, there is no specific drug for *W. bancrofti.*

Antimony compounds, especially *anthiomaline* (p. 825), when injected intravenously, diminish the number of circulating microfilariæ, but have apparently no effect upon the parent worms. Kingsbury claimed that, when injected into enlarged inguinal glands, anthiomaline is effective in reducing the size and stopping inflammatory attacks, and that it may also arrest the development of elephantiasis.

Prophylaxis of filarial disease.—The prevention of filarial disease resolves itself into anti-mosquito measures and protection from mosquito-bite. Unprotected wells, tanks or stagnant pools must not be permitted in the neighbourhood of dwelling-houses. All vessels used for storing water should be emptied at least once a week. The mosquito-net is indispensible in filarial as well as in malarial countries. In the Pacific Islands, especially in the Gilbert and Ellice group, considerable reduction of filarial incidence has taken place following O'Connor's recommendation to cut down the thick undergrowth, thus giving passage to the Trade Winds which blow away the mosquitoes (*Aëdes variegatus*[1]). Burning empty coconut shells and filling up holes and cavities in the trunks of the coconut trees has been beneficial, as it destroys breeding places.

Sweet and Pillai conducted a successful campaign against the intermediary mosquito of *Wuchereria malayi—Mansonioides annulifera,* and the water lettuce *Pistia stratiotes,* to which the larvæ become attached ; they succeeded in clearing this plant from North Travancore, with the consequent elimination of filariasis from that area. The species of *Mansonioides* which act as vectors in Malaya flourish in association with the roots of swamp trees. The methods adopted in Travancore, therefore, cannot be applied to Malaya. (*See* p. 972.)

---

[1] Also known as *A. scutellaris.*

The subjects of filariasis should be regarded as dangers to themselves and to the community, and be compelled to sleep under mosquito-nets.

II. FILARIASIS DUE TO LOA LOA

History and geographical distribution.—The embryonic form (microfilaria diurna), which closely resembles microfilaria bancrofti, was described by Manson in 1891; the patient from whom the specimen of blood was derived had formerly had an adult *Loa loa* in his eye. Later, association was established between *L. loa* and the disease known as Calabar swellings, and also between that disease and microfilaria diurna.

Loa loa is widely distributed in West Africa from Sierra Leone to Benguella, and is especially common in the Cameroons and on the Ogowe River; its distribution is, however, mainly confined to the coastal plains, and follows the course of the Congo and its tributaries to a point about 1,500 miles from its mouth (Map VI). This parasite is also found in the Southern Sudan between the Bahr el Ghazal and the Belgian Congo between latitudes 4° and 6° N. and longitudes 27° and 31° E.

Ætiology.—A description of the adult *Loa loa* is given in the Appendix, p. 933. Here it suffices to say that it is 30 mm. or more in length, the female being, as a rule, considerably longer than her partner (Fig. 169.). The cuticle is embossed with numerous characteristic protuberances.

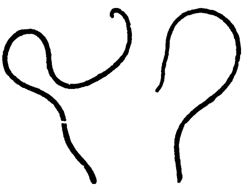


Fig. 169.—*Loa loa* Nat. size.

Structure of the embryonic form.—Microfilaria loa (= diurna) is very similar in size (298 μ by 7·5 μ) and structure to microfilaria bancrofti. Like the latter, it is enclosed within a "sheath," its tail is pointed, and it has the same V-and tailspots. (Fig. 146, *2*, p. 704.)

The periodicity is the exact reverse of that of microfilaria bancrofti, for the embryos appear in large numbers in the peripheral blood during the daytime and disappear at night. The periodicity is, in fact, *diurnal* (Chart 29).

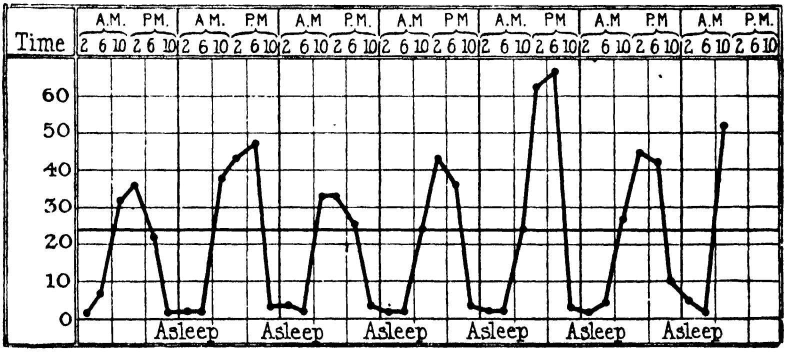


Chart 29.—Diurnal periodicity of microfilaria loa (mf. diurna).

The numbers in the first column are those of the microfilariæ per 16 c.mm. of blood.

The respective periodicities are very characteristic—more so, apparently, in microfilaria loa than in microfilaria bancrofti; for, whereas by inverting the sleeping habits of a subject of *W. bancrofti* infection it is easy to invert or disturb the periodicity of the microfilariæ, this has not been done so easily with microfilaria loa, although several experiments have been made. It does, however, take place gradually, as for instance when the patient travels round the world. (Külz, 1914). In Americans who have been infected in West Africa, the microfilariæ maintain their periodicity on their return home. A series of important observations on the mechanism of periodicity were made by Gönnert, who was transfused with blood from a patient heavily infected with *L. loa* and *M. perstans*, whose blood contained 1,640,000 of the former and 112,000 of the latter per 160 c.c. Subsequently, microfilariæ loa were demonstrated in the recipient's blood and maintained a strict diurnal periodicity for three days. Most of the microfilariæ perstans disappeared from the blood within the first few days, but *some persisted for at least three years.* Somewhat similar results were obtained with microfilaria bancrofti by Knott and Hawking.

Life-history.—In early editions of this work Manson called attention to the mangrove fly, *Chrysops dimidiata* (Fig. 371, p. 978), as a possible intermediary, on account of its diurnal and blood-sucking habits and local distribution. This conjecture Leiper, and later Kleine and Connal, have ascertained to be well-founded. Development takes place in the thoracic muscles and fat-body of *C. dimidiata* and *C. silacea*, and in the Southern Sudan probably in *C. distinctipennis*.

After the larva has entered the human body, development seems to be very slow, and probably full maturity is not attained until after several years. In many cases the parasite does not show itself until three, four, or four and a half years after the patient has left the endemic area. In one case it was extracted from the eye thirteen years after the patient had left Africa ; in another, the worm or worms appeared at irregular intervals during fifteen years, and the Editor has records of finding live microfilariæ in the blood for a period of seventeen years. Manifestly it is long-lived. An interesting and suggestive evidence of slow development is that, while the immature active worm is often seen in children, the embryonic form in the blood is found as a rule only in adults, it may be as long as seven years from the time of the original infection.

This slow development of *L. loa* seems to account for the very frequent failure to find the microfilariæ in the blood in cases from which mature parasites have been extracted, a circumstance which has been brought forward as an argument against the theory that the diurnal microfilaria is really the offspring of *L. loa*.

As yet it is impossible to estimate accurately the number of adult worms present in any given infection, although in advanced cases some idea might be obtained from the number of microfilariæ in the peripheral blood. As a rule, it is safe to conclude that the particular loa that may show itself about the eye or elsewhere is only one of many. Thus, in 1903, Brumpt, at the autopsy of a negro whose blood contained microfilariæ, found in the tissues of the heart five adult worms. Four of these were cretified, but the fifth was alive and contained embryos similar to those in the blood.

Pathology.—*L. loa*, during the period of its growth and development in man, makes frequent excursions through the subdermal connective tissues. It has been noticed very often beneath the skin of the fingers, and it has been excised from under the skin of the back, from above the sternum, from the left breast, the lingual frænum, the loose skin of the penis, the eyelids, the conjunctiva, the anterior chamber of the eye, and also the scalp. The parts most frequently mentioned are the eyes, and, although the worm may attract more attention in this situation, it does seem as though it had a decided predilection for the eye and its neighbourhood (Fig. 170). A patient of Manson's once stated that the average rate at which a loa travelled was about an inch in two minutes. Both he and others have observed that warmth, such as sitting before a fire, seems to attract them to the surface of the body. Chesterman on the Congo reported finding live adult worms in 10 per cent. of all cases operated upon for hernia and elephantiasis. Cretified worms, too, are frequently encountered. Whether alive or dead, this parasite evokes a high eosinophil response, and an increase to 30, 40, and even higher percentages, is common in Europeans who have resided in the endemic districts in Southern Nigeria, the Congo and Cameroons..

Symptoms.—As a rule, the migrations of the parasite give rise to no serious inconvenience, but they may cause prickings, itching, creeping sensations and, occasionally, transient œdematous swellings (Calabar swellings) in various parts of the body. When the parasite appears under the conjunctiva it may cause a considerable amount of irritation and congestion ; there may even be actual pain, associated with swelling and inability to use the eye and, perhaps, tumefaction of the eyelids (Fig. 171). Should a loa wander into the rima glottidis, or the urethra, the consequences might be serious, and great pain is sometimes caused. Occasionally, too, as Chesterman recorded, the death of the parent worm may cause a localized abscess in the groin or axilla.

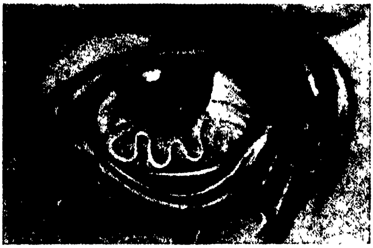


Fig. 170.—Loa loa in the eye.
(*After Fülleborn.*)

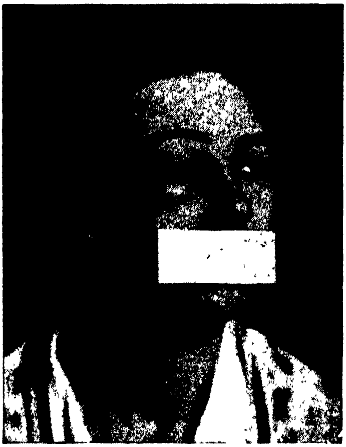


Fig. 171.—Calabar swelling of right eye.

Calabar Swellings

Under this name Thompstone originally described certain fugitive swellings which are frequent in natives and Europeans alike in parts of tropical West Africa. The swellings are about the size of half a goose egg, painless, though somewhat hot, both objectively and subjectively, not pitting on pressure, and usually disappearing in about three days. They come suddenly and disappear gradually, and occur in any part of the body. One swelling occurs at a time, but recurs at irregular intervals and, perhaps, for many years after the patient has returned to Europe. In some instances the swellings seem to be due to rubbing provoked by the irritation accompanying the presence of a loa just under the skin; in other instances they develop spontaneously. In the hand or forearm they may give rise to a sensation of powerlessness and soreness, as if the part had received a blow. They never suppurate. (Fig. 172.)

Although in a large proportion of cases *L. loa* embryos cannot be found, in a number of others either the parent worm has shown itself in the eye or its microfilariæ have been detected in the blood. This discovery, together with the geographical endemicity of these swellings and their clinical characters, makes it practically certain that they are produced by *L. loa*. Manson believed that the swellings might be caused by the emission of her larvæ by a parent loa into the connective tissue, but it was proved by Fülleborn that they represent an allergic reaction on the part of the tissues in response to filarial toxins.

Fig. 172.—Calabar swelling on dorsum of hand in a European lady from the Congo.

The recurrence of Calabar swellings on the arm or leg appears to give rise to induration of the fascia and connective tissue round the tendon-sheaths. In two cases the Editor observed permanent circular cyst-like swellings which may cause pain on muscular movement. Apparently, they are attached to the tendon-sheaths and muscular aponeuroses. Solid œdema of one leg persisting for six weeks has been observed in a European from West Africa who had been infected for a number of years; hydroceles also have been recorded (Fig. 173.)

Urticaria and *dermatitis* of a particularly irritating form are sometimes found in filaria cases. The dermatitis is analogous to that found in onchocerciasis. As in infection with *W. bancrofti*, multiple intramuscular abscesses, due to secondary infection by staphylococci or streptococci, and even purulent infections of the hip-joint may sometimes be found in association with *Loa loa*.

Diagnosis.—The microfilariæ can be demonstrated in the blood, or the high eosinophilia (30–60 per cent.) suggests this parasite. Confirmatory evidence can be obtained by the intradermal or complement-fixation tests (p. 717). An antigen prepared from the filariæ of the South American ostrich (*Contortospiculum rheæ*) gives good results. These reactions are generally more marked and reliable than in *W. bancrofti* infections; it must be emphasized that a diagnosis of *L. loa* has often to be made when no microfilariæ are present, for they may not appear in the peripheral blood for several years after the original infection.

Treatment. — Calabar swellings are notoriously difficult to treat effectively. The irritation can best be allayed by evaporating lead lotion, or by *heliobrom* (dibromotannate of urea) in alcohol. Fairley employed a desensitization method with increasing strengths of *Dirofilaria* antigen, from 0·5 c.c. of the extract in normal saline, gradually increasing to 5 c.c. or more, and he had some success. De Choisy and others asserted that this infection may to some extent be controlled by injections of tartar emetic; and that in some cases Calabar swellings can be treated by intravenous anthiomaline injections every other day (3 c.c. of a 6 per cent. solution).

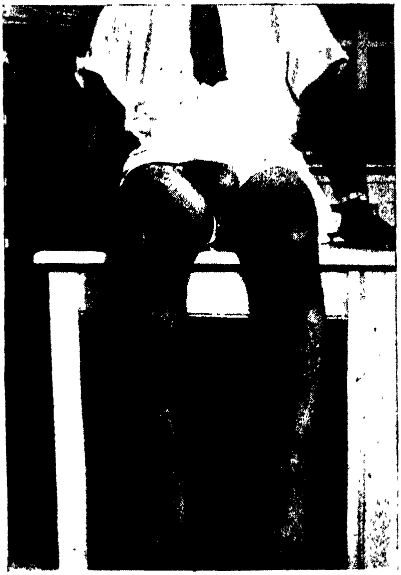


Fig. 173.—Hydrocele and solid œdema of right leg in *L. loa* infection from West Africa.

III. HUMAN ONCHOCERCIASIS

History and geographical distribution.—*Onchocerca volvulus* was originally discovered by a German medical missionary in negroes of the Gold Coast. The contained parasite was named *Filaria volvulus* by Leuckart in 1893. Blanchard, in 1899, demonstrated the parasite lying in a lymphatic space in a tumour. It occurs sporadically throughout the whole of the Congo basin, but especially on the Oellé, Kibali and Itimbiri rivers. It has been observed in Nigeria (Best and Parsons), in the Camerooms, (Fülleborn), in Senegal and French Guinea (Clapier), in Uganda (Cook), in Togo, Dahomey and Ivory Coast, in Kenya (Kakamega and Southern Kavirondo), in Tanganyika, in Nyasaland, and in the Southern Sudan (Bahr-el-Ghazal,—Bryant) (Map VI).

In 1915 Robles described *O. volvulus* as being common in Guatemala. Caldéron (1920) defined the endemic zones as being in the departments of Sacatapéquez, Escuinthla, and Solola, at an altitude of 2,800–3,600 ft. It is suggested that the parasite was imported by negro slaves from Jamaica, though Brumpt regarded the S. American worm as a distinct species—*O. cœcutiens*, " the blinding filaria "—mainly on account of its association with a curious punctate keratitis, minor distinctions in the morphology of the male parasite, predilection of the tumours for the head, and endemic zone of the disease at an altitude of 600–1,200 metres. De la Torre described onchocerciasis in Mexico, over 15,000 cases in the State of Chiapas and 5,000 in Oaxaca being known. On the other hand, Strong, Sandground, and Bequært (1934), in their monograph on onchocerciasis in Central America, demonstrated that *O. volvulus* and *O. cœcutiens* are morphologically identical. In Guatemala, onchocerciasis occurs endemically in those districts in which coffee is grown, from 2,800–3,000 ft., especially amongst the Indian population.

Fig. 174.—Onchocerciasis from the Congo. Typical nodules on knees, elbows and scalp.
(*Dr. C. C. Chesterman.*)

Ætiology.—The worms are white and filiform, tapering at both ends. They vary considerably in length, the female, as in all the filariæ, being much the longer (35–40 cm.). At least four males and two females are present in every tumour. The unsheathed embryos measure about 300 μ in length. Macfie and Corson found that in the Gold Coast natives microfilariæ are commonly encountered in sections of the skin, but some of the embryos, they believe, are referable to a new species, *Agamofilaria streptocerca* (*see* p. 938), distinguishable from those of *O. volvulus*. The presence of the microfilariæ of *O. volvulus* in the skin is associated in some with a lichenoid condition.

Life-history.—Embryos, presumably those of *O. volvulus*, have been found in the peripheral circulation by Fülleborn, Simon, Ouzilleau, and Rodenwaldt; but usually the microfilariæ occur round the periphery of the tumours, and are ingested by the jinja-fly (*Simulium damnosum*), in the thoracic muscles of which they undergo a development similar to that of *W. bancrofti* (Blacklock). In Kenya the species is *S. neavei* (Buckley). In South America the insect intermediary hosts are *Eusimulium avidum* (*metallicum*), *E. ochraceum* and *E. mooseri*.

Gibbins and Lœwenthal showed that in Victoria Nyanza district of Uganda distribution of cutaneous onchocerciasis amongst the natives coincides with that of *Simulium damnosum*.

Pathology and symptoms.—*O. volvulus* is found in peculiar subcutaneous fibrous tumours, the size of a pea to that of a pigeon's egg. The same patient may present one or several of these tumours (Fig. 174). The regions of the body most frequently affected are those in which the peripheral lymphatics converge. Thus, the tumours are usually found in the axilla, in the popliteal space, above the elbow, in the suboccipital region, and in the intercostal spaces. In their incipient stages they cause very considerable pain. Periodic recurrences of symptoms are attributable, according to native belief, to the lunar cycle, occurring almost every fifteen days. In the South American form the occipito-frontal and temporal regions are most usually affected. Strong found in Ste. Emilia, Guatemala, 54 per cent. of the inhabitants infected.

The tumours are situated on the head, usually the scalp, and measure 6–20 mm., rarely as much as 30 mm. They may cap the skull, and from them the adult worms may be obtained entire by digesting the tissues with papaya juice or papaine in 0·2 per cent. HCl. The tumours are never adherent to the surrounding structures and can be easily enucleated. They are formed of a dense mass of connective tissue, which enwraps the parasites and encloses small cyst-like spaces filled with a greyish viscous substance consisting almost entirely of microfilariæ. The position of the adult worms within these tumours is very remarkable. The greater length of the coiled-up bodies of the females is embedded in the connective stroma; consequently they can only be extracted in fragments.

Though they are most commonly found in adults of mature years, Strong saw *volvulus* tumours in a child of two months, and found that they often give rise to neoplasms. Sometimes, however, especially in Europeans, the embryos may exist in large numbers in the skin without any palpable nodules.

Robles reported that tumours of the scalp and periosteum may produce epileptiform attacks in Colombia, due to perforation of the cranium. Erysipelatoid skin-rashes (known as "*Erisepela de la costa*") are common in the South American form.

Lymphatic enlargement of the scrotum, hydroceles and enlarged testes were noted by Dyce Sharp in patients infected with *O. volvulus*, while the embryos can be demonstrated in hydrocele fluid, as well as in œdematous lymphatic tissue. On the Congo, Ouzilleau and Chesterman described elephantiasis of the scrotum and legs in association with this parasite. As in *W. bancrofti* infections, localized abscess formation also occurs, and several dead female worms have been removed from abscesses. The elephantoid scrotum due to *O. volvulus* is convoluted like a brain, and the subcutaneous tissue is more solid and less œdematous than that in elephantiasis attributed to *W. bancrofti*, while the embryos are found in the skin. Harris in Kenya noted a tendency to the formation of lipomata.

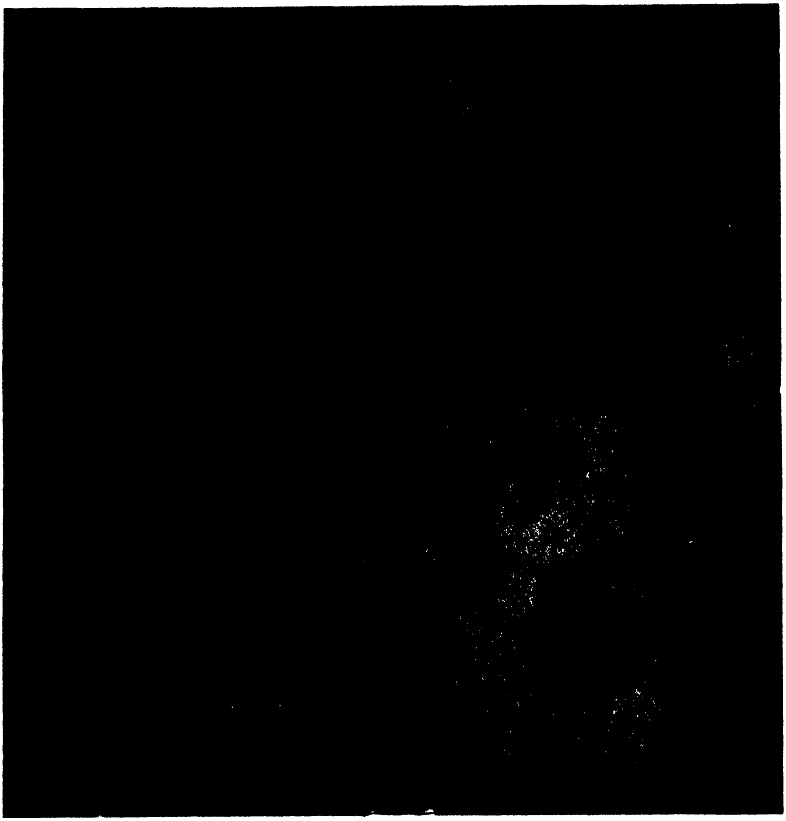


Fig. 175.—Lichenoid eruptions of onchocerciasis. (*After Fulleborn.*)

Déjou (1939) described acute arthritis in onchocerciasis in French West Africa. Microfilariæ can be demonstrated in the synovial fluid obtained by joint puncture, which should be examined soon after withdrawal. In these cases filarial nodules can be found in the cruro-inguinal region, in the popliteal spaces, and on the costal margins.

Skin symptoms.—Dermatitis (xeroderma) or lizard skin (Rodhain and Dubois) is commonly associated with *O. volvulus*. The skin affection is described by some as *lichenoid* and is more easily visible on the back

(Fig. 175). It is usually seen in South American cases, but shows up much better in Europeans than in dark-skinned natives. The skin is thickened as well as wrinkled. Fülleborn described cases in German colonists from Mexico. This complication was termed *lichen* by Macfie and Corson and *scleroderma* by Ouzilleau in West Africa.

Recurrent inflammations of the skin of the face often result in enlargement of the pinna of the ear. Associated with this there is a definite dermatitis, with discoloured patches of skin on the neck and back, and xeroderma, especially of the elbows. The patient experiences terrible pruritus, especially at night. Quite commonly he suffers from photophobia and some aberrations of vision, and there is usually an eosinophilia of about 35 per cent.

Several onchocerca nodules can usually be found in the deep subcutaneous fascia, and when excised, the adult worms can be demonstrated, and living embryos also, by teasing a snippet from the surrounding skin in normal saline (Fig. 176).

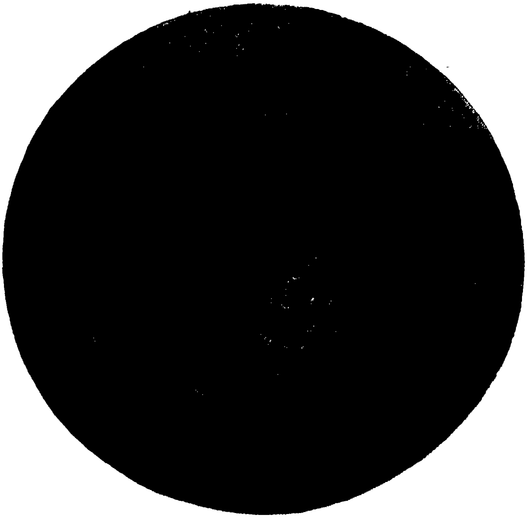


Fig. 176.—Microphotograph of microfilaria of *O. volvulus* in subcutaneous tissue. Note absence of tissue reaction.
(*Photograph by Dr. P. H. Martin*)

Eye lesions.—In 1918 Pacheco Luna suggested that *O. volvulus*, in its migrations through the body, was responsible for a peculiar form of keratitis punctata commonly found in Guatemala. Calderon claimed that it produces lesions of the iris and cornea as well. Similar eye lesions were described amongst the Congo negroes by Hissette. Photophobia, xerosis and impaired vision result, or the pupil may become obliterated and complete blindness ensue. Interstitial keratitis, keratitis punctata and uveitis associated with pannus are other lesions. Keratitis punctata is not regarded as specifically characteristic, but as an epiphenomenon (Fig. 177). In the acute stage eye lesions are associated with erysipelas of the face and ear, neuralgia and pyrexia. The chronic form is characterized by œdema of the face and a greyish pigmentation of the skin. Skin symptoms have periods of exacerbation every fifteen days. Further studies on the eyes were made by Strong and Sandground in Guatemala (1934). In Kenya, Hawking in the Kakamega district found microfilariæ in the skin in 62 per cent. of a group with eye lesions or nodules. Eye lesions were present in 84 per cent. of those with microfilariæ and in 23 per cent. of those without.

Silva found microfilariæ in the choroid and the posterior two-thirds of the cornea in sections of the eyes, and this was confirmed by demonstrations of living microfilariæ creeping on the corneal surface. They can be found, too, in the anterior chamber and in the iris, as they are phototropic. Boase (1935) and also Mexican ophthalmologists identified them by the corneal microscope. Entropic vision of the embryos crossing the visual fields is said to be by no means uncommon. The pannus of onchocerciasis and pigmented choroido-retinitis ultimately produce blindness, as described by Hissette. Two cases of blindness in Europeans from Kenya have been recorded in recent years. In both, in spite of all methods of treatment, pannus steadily progressed. In neither were palpable tumours demonstrable. Removal of operable tumours does not eradicate the disease, because new ones form. In Mexico City, where the disease cannot spread, microfilariæ can still be found in the skin years after widespread excision of nodules. Eye lesions are late manifestations of onchocerciasis, and are rarely seen in children.

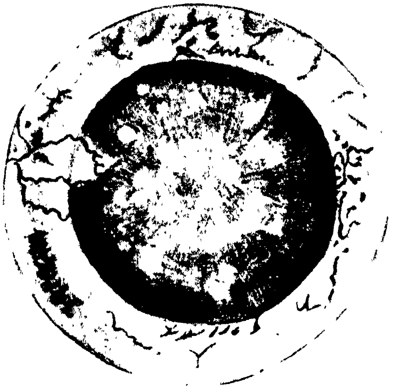


Fig. 177.—Ocular onchocerciasis from the Congo, showing punctate keratitis and lateral formation of pannus. (*Hissette.*)

The greater the distance between the eyes and the localization of the adult parent filariæ, the longer is development of eye lesions delayed.

Diagnosis.—The diagnosis is made by snipping off a piece of skin with forceps near a nodule, placing it in saline solution for 15 minutes at 37° C., centrifuging and then pipetting off the bottom layer with the microfilariæ which have escaped from the tissues. The embryos are thermostatic, and are attracted by heat to the surface of the skin ; thus, demonstration is best effected by placing hot fomentations on the skin, and then taking off shavings by means of a Thiersch razor. When these are placed in warm physiological saline solution, embryos can be detected. Howard recommends placing a powerful electric light bulb a few inches from the skin. No local anæsthetic must be used, and freezing is especially contra-indicated.

Intradermal tests.—These tests were carried out by Fülleborn and by Rodhain and Dubois with dirofilaria antigen (*see* p. 717). The results have not been as satisfactory as in other filarial infections.

Complement-fixation reaction in onchocerciasis.—Van Hoof employed a complement-deviation test for onchocerciasis, based upon the same principles as other similar tests in filariasis, and he considered that it had done much to remove uncertainties regarding the pathogenic action of this parasite.

The tightly-packed mass of adult parasites is retained when dissected out of the cyst. The filariæ are then cut into thin slices and placed in a desiccator over sulphuric acid, and when dry they are extracted with ether at 25° C.—a process which occupies several days—and are subsequently dried and extracted with alcohol for ten days. The best extracts have an antigenic titre of 1 in 25. It is claimed that the test when put up by the Calmette-Massol technique is so specific that neither *Loa loa*, *A. perstans*, nor intestinal helminths are able to vitiate it. The antibodies thus demonstrated are present in serum, cerebrospinal fluid, synovial fluid and œdematous exudates.

The observations so far made on the positive reactions by this test are in favour of the view that certain forms of elephantiasis in the Congo are manifestations of onchocerciasis.

Eosinophilia is not usually marked in onchocerciasis and is therefore not useful as a diagnostic sign.

Treatment.—In the African form the tumours appear to be painless, and may be removed by excision. In the South American form, removal of the tumours under cocaine anæsthesia is said to be followed by an improvement in the ocular conditions within a week or so. Adams (1938) stated that in a European from the Katanga province of the Congo intravenous injections of neostibosan arrested progress of the corneal opacities, but, in a comparable case observed by the Editor, no improvement was noted, so that antimony therapy had to be discontinued. Harris, who gave sodium antimony tartrate intravenously, noted that the microfilariæ disappeared from the skin, in some cases rapidly, when the treatment was continued over a period of four weeks. Some benefit was also observed in ocular and skin lesions when protein shock therapy was employed. Hoffman stated that atebrin in large doses has achieved a reputation in Mexico as a valuable therapeutic agent. A useful application to alleviate pruritus is *heliobrom* (dibromotannic urea) 10 per cent. in spirit, applied to the skin at night.

IV. DRACONTIASIS

Synonym. Guinea-worm.

Geographical distribution.—This important parasite, *Dracunculus medinensis*, is found in certain parts of Africa and India, and appears to have been imported from America. In Africa it occurs in the Valley of the Nile, Lake Chad, Bornu, and West Africa; it has been observed in Uganda, but not in the Congo basin. It is also found in Persia, Turkestan, Arabia, and in a very limited part of Brazil (Feira de Santa Anna). Formerly it was supposed to be endemic in Curaçao, Demerara, and Surinam. Dracunculus is not equally diffused throughout this extensive area; it tends to special prevalence in limited districts, in some of which it is excessively common. In parts of the Deccan, for example, at certain seasons of the year nearly half the population is affected; and in places on the West Coast of Africa nearly every negro has one or more specimens about him. In Europe, guinea-worm is seen only in natives of, or in recent visitors from, the endemic areas. In North America, according to Chitwood, it has been found in the silver fox (*Vulpes fulva*), the racoon (*Procyon lotor*), and the mink (*Putorius vison*), but never in man. In Asia and Africa the parasite is widespread amongst carnivora.

Ætiology. *The parasite.*—The male worm has only rarely been found (*see* p. 940). The female measures about 32·5 cm. to 1 m. 20 cm. in length, by 1·5 mm. in diameter. The embryos are somewhat flattened, with a tapering tail, and measure 0·5–0·75 mm. in length by 0·017 mm. in breadth.

Life-history.—The embryos of *D. medinensis* are shed into water and, swimming about actively, enter the body-cavity of a fresh-water crustacean, *Cyclops quadricornis*, or allied species, in which they develop until a length of 1 mm. is attained. (For details, *see* Appendix, p. 941.)

Mode of infection.—The metamorphosis of *D. medinensis* in cyclops was discovered by Fedchenko in Turkestan and subsequently confirmed by Manson in England; but, owing to the colder climate of this country, the metamorphosis takes longer to complete—eight or nine weeks, instead of five weeks as in Turkestan. Fedchenko supposed that cyclops, containing the larvæ of the guinea-worm, was swallowed by man in drinking-water, digested, and the parasite, being then set free, worked its way into the tissues of its new and definitive host.

Later, Leiper showed that when an infected cyclops is transferred to a 2·0 per cent. solution of hydrochloric acid it is immediately killed, but the larvæ, so far from being destroyed, are aroused to great activity, and eventually escape into the fluid, in which they swim freely. From this he conjectured that under natural conditions man becomes infected through the ingestion of cyclops containing these worms, the gastric juice acting on cyclops and larva in the same way as the hydrochloric acid in his experiment. In order to prove this, he fed a monkey on bananas concealing cyclops which had been infected for five weeks, and which contained fully-developed larvæ. Six months later, when the monkey died, five worms were found in its connective tissues, all possessing the anatomical characteristics of *D. medinensis*.

The evidence is now fairly complete that the life-span of the female dracunculus, before she appears on the surface of the body, extends to about one year. It is not to be supposed that every species of cyclops is an effective intermediary; if this were the case, guinea-worm infection would have a much wider geographical range.

Pathology and symptoms.—The parasite, on attaining maturity, makes for the legs and feet; these are the parts of the human body most likely, in tropical countries, to come in contact with puddles of water, the medium in which cyclops—the intermediary host—lives. The water-carriers in India are very subject to guinea-worm, which, in their case, appears on the back—that is, the part of the body against which the water-skin lies when being carried. It seems that the mature guinea-worm, by instinct, seeks out that part of the body most in contact with water.

Occasionally, the guinea-worm fails to pierce the integument of her host; sometimes she dies before arriving at maturity. In either case she may give rise to abscess; or she may become cretified, and in this condition may be felt, years afterwards, as a hard convoluted cord under the skin, or be discovered on dissection.

The haunt of the female guinea-worm is the connective tissue of the limbs and trunk. When mature, she proceeds to bore her way through this tissue, travelling downwards. In 85 per cent. of cases she presents in some part of the lower extremities; occasionally in the scrotum or on the sole of the foot (Fig. 178); rarely in the arms; exceptionally in other parts of the body, or even in the head. In a proportion of cases the appearance of the worm at the surface of the body is preceded by slight fever and urticaria; the onset of the skin eruption is generally at night, before the blister or other localizing signs are noted. Arrived at her destination, the female worm pierces the derma. In consequence of some irritating secretion, a small blister, containing, as a rule, numerous embryos, forms and elevates the epidermis over the site of the hole in the derma. The irritation due to this act causes a burning sensation and induces the patient to immerse his foot in water. By and by the blister ruptures, disclosing a small superficial erosion $\frac{1}{2}$-$\frac{3}{4}$ in. in diameter. At the centre of the erosion, which sometimes quickly heals spontaneously, a minute hole, large enough to admit an ordinary probe, is visible. Occasionally, when the blister ruptures, the head of the worm is seen protruding from this hole; as a rule, however, at first the worm does not show. If the neighbourhood of the ulcer is douched with a stream of cold water from a sponge, in a few seconds a droplet of fluid—at first clear, later milky — wells up through the hole and flows over the surface. Sometimes, instead of this fluid, a small, beautifully pellucid tube, the uterus, about 1 mm. in diameter, is projected through the hole in response to the stimulus of the cold water. Apparently in this act the tissues of the head are exploded in order that the uterus may escape (Fig. 179).

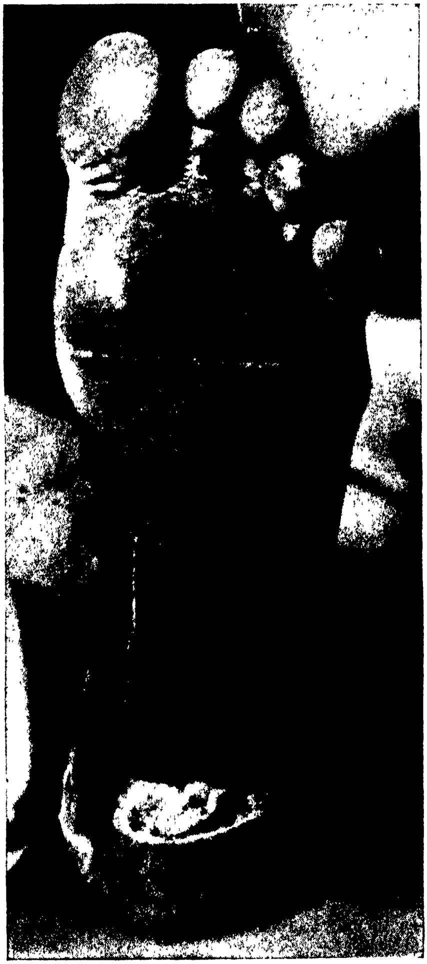


Fig. 178.—Guinea-worm emerging from sole of foot.

When the tube has been extruded an inch or thereabouts, it suddenly fills with an opaque whitish material, ruptures, and collapses, the fluid spreading over the surface of the erosion. If a little of the fluid, either that which has welled up through the hole, or that which has escaped from the ruptured tube, be placed under the microscope, it is seen to contain myriads of dracunculus embryos lying coiled up, almost motionless, with their tails projecting in a very characteristic manner (Fig. 180). If now a drop of water be instilled below the cover-glass, the embryos unroll themselves, and, in a very short time, swim about, *more suo*, with great activity. If the douching be repeated after an hour or longer, a further supply of embryos can be obtained ; and this can be continued from time to time until the worm has emptied herself. Apparently the cold applied to the skin of the host stimulates the worm to contract, and thereby force out her uterus, inch by inch, until it is completely extruded. The repeated birth of a limited number of progeny each time the skin of the host comes into contact with water is therefore a wonderful provision of nature. Aberrant forms of embryos were described by Moorthy and Sweet (p. 940).

The first symptoms appear usually simultaneously with the beginning of the blister-formation, and consist of urticaria, nausea, vomiting, diarrhœa, asthma, giddiness and fainting and they are believed to be due to absorption of the toxin emitted by the worm to form the initial skin blister. The symptoms strongly suggest an anaphylactic reaction, and goats injected with guinea-worm extracts show similar symptoms, while injections of adrenalin bring about rapid improvement. Later symptoms result from the invasion of the ulcer by bacteria.

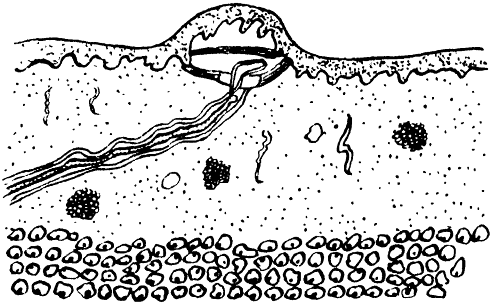


Fig. 179.—Diagram of vesicle caused by guinea-worm, showing prolapse of the uterus in the act of discharging embryos into the blister cavity.
(*After Fairley and Glen Liston.*)

Should the worm become injured or lacerated while lying in the subcutaneous tissues, severe local reaction may develop. The part becomes extremely painful, inflamed and œdematous, and cellulitis may result, due to secondary downward growth of staphylococci and streptococci from the skin. Arthritis, synovitis, epididymitis, contractions of tendons, and ankylosis of joints have even been known to ensue. In some patients, generalized systemic symptoms accompany the premonitory urticaria, such as pyrexia, giddiness, dyspnœa and vomiting ; and gastro-intestinal symptoms have been noted during the early stages of guinea-worm infection, associated with an increase of eosinophil cells in the blood ; this is due to the absorption of a specific toxin, so that alarming symptoms may be produced in laboratory animals by intravenous injection of extracts of the adult dracunculus.

That the cellulitis associated with guinea-worm is due to the excretion of toxins by the mature parasite was shown by Fairley and Glen Liston, who failed to produce any local or general reaction by subcutaneous injection of the embryos themselves. Botreau-Roussel and Huard described a specific non-bacterial arthritis, especially of the knee-joint, associated with the presence of a guinea-worm in the vicinity.

Lester from Dar-es-Salaam reported the discovery of an entire guinea-worm coiled in a hernial sac; it was kept alive in the laboratory for twelve days after removal. According to Trewn, guinea-worms may present themselves after as long an interval as fifteen years from the time of infection. Massive infections are also reported, and as many as 56 adult worms have been counted in one person at the same time.

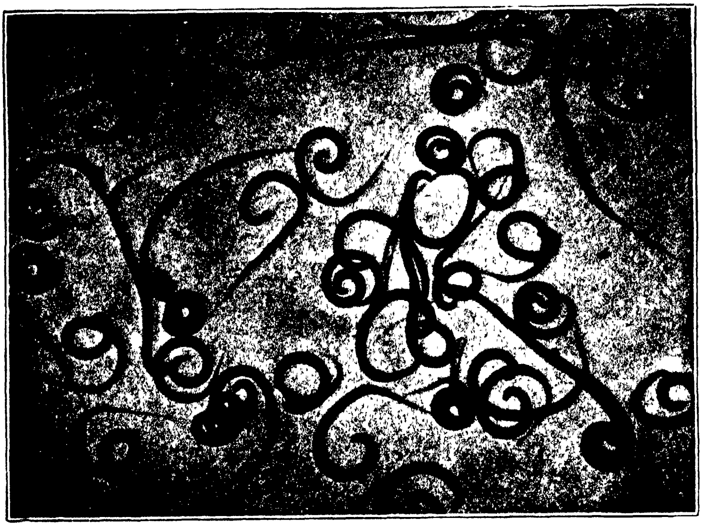


Fig. 180.—Embryos of *D. medinensis.* (*Microphotograph by Mr. H. B. Bristow.*)

Diagnosis.—This is, as a rule, sufficiently obvious. In cryptic infections there is generally an eosinophilia. If the worms cannot be seen they may be felt underneath the skin. When both these methods fail, screening with X-rays has been of use; and injection of 2 c.c. of 10 per cent. collargol into the worm renders it opaque (Hudellet, 1919). Effete and calcified worms are easily demonstrated by skiagraphy. (Plate XXI.)

An *intradermal test* for diagnostic purposes was introduced by Ramsay. The antigen is obtained by adding to 100 c.c. of ether 0·25 grm. of dried powdered guinea-worm, with frequent shakings at room temperature for two hours to remove the lipoids. The dried, ether-free residue is extracted with shaking for four hours, in 100 c.c. of 0·85 per cent. solution of sodium chloride at 37° C. After centrifugation, it is passed through No. 6 Seitz filter, and 0·25 c.c. of this is used for injection. A positive wheal is 2–3 cm. in diameter, with outrunners.

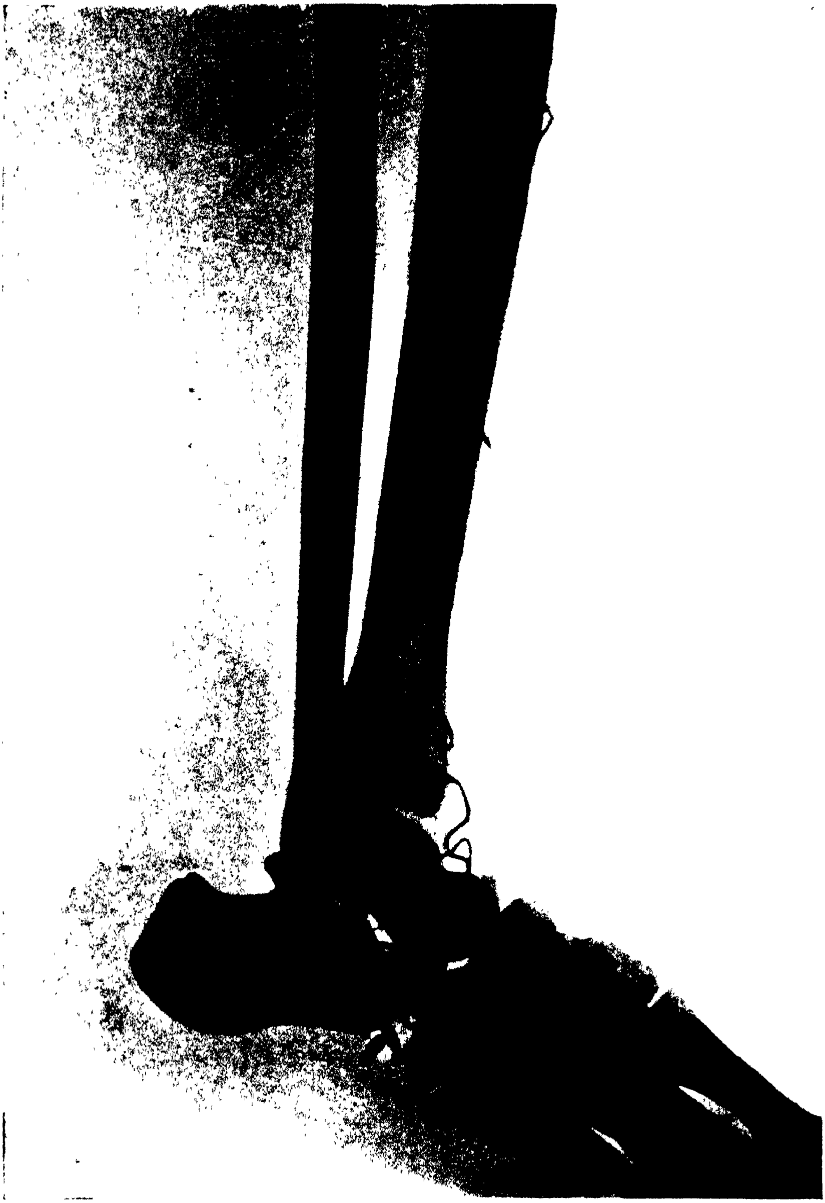
Sequelæ.—Subacute sterile abscesses are occasionally seen, due to premature death of the female *D. medinensis*, with the liberation of embryos into the subcutaneous tissue. The condition is diagnosed by the deeply situated fluctuating swelling, not communicating with the exterior. In synovitis and arthritis, the exudate may be serous or purulent. Generally, there is an associated cellulitis, the synovial membrane being involved by direct spread through the adjacent tissues. Permanent deformities and a history of prolonged illness in the recumbent position are invariably associated with sepsis. Bony ankylosis is rare. The joints mainly involved are the knee and the ankle, while the tendo Achillis and hamstrings are not infrequently contracted. Connor (1922) drew attention to cases diagnosed as chronic rheumatism, traumatic synovitis, periostitis or sciatica, where X-ray examination revealed calcified worms.

Treatment.—Formerly it was the custom, as soon as a guinea-worm showed herself, to attach the protruding part to a piece of wood and endeavour to wind her out by making a turn or two daily. Sometimes these attempts succeeded ; just as often the worm snapped under the strain. The consequences of this accident were often disastrous. Myriads of young escaped from the ruptured ends into the tissues, and violent inflammation and fever, followed by abscess and sloughing, ensued ; weeks, or months perhaps, elapsed before the unhappy victims of this rough surgery were able to get about. Too often, serious contractions and ankylosis from loss of tissue and inflammation, and even death from septic trouble, resulted.

If a guinea-worm be protected from injury, and the part she occupies frequently douched with water, her uterus will be gradually and naturally forced out inch by inch and emptied of embryos. Until this process is completed she resists extraction. When, in from fifteen to twenty days, parturition is completed, which can easily be ascertained by the douching experiment, the worm is absorbed or tends to emerge spontaneously. A little traction then may aid extrusion. Traction, however, must not be employed so long as embryos are being emitted. When located by X-rays and collargol, the worm may be dissected out (Hudellet).

The parasite may also be killed by injecting her, by means of a syringe, with solution of bichloride of mercury, 1 in 1000 ; after twenty-four hours, extraction is usually easily effected. If the worm has not shown herself externally, but can be felt coiled up under the skin, the coils should be injected, through several punctures, with a few drops of the same solution. Fairley and Glen Liston advocated aspiration of the blister-fluid before extraction, followed by precautions to avoid sepsis. The surface should first be painted with tincture of iodine. After a period of forty-eight hours, they advised excision of the worm if lying convoluted in a limited space ; failing this, intermittent traction should be combined with massage. The subcutaneous injection of 9–10 min. of 1 in 1000 adrenalin hydrochloride immediately relieves the distressing prodromal symptoms, such as uricaria and asthma, from absorption of toxins.

To complete extraction of the worm, the operative procedure is as follows. It is applicable whether a blister has formed or not, or whether a sinus is present. The skin overlying the worm at some distance from the ulcer is infiltrated with cocaine and adrenalin (2 c.c. of 1 per cent. cocaine and 1 c.c. of 1 in 2000 adrenalin).



Radiograph of leg showing guinea-worm injected with lipiodol.

(*Dr. Botreau-Roussel.*)

GUINEA-WORM.

PLATE XXI

RADIOGRAPH OF CALCIFIED CYSTICERCI IN THE THIGH.

An incision is made at right angles to the line of the worm through the anæsthetized tissues. The whitish fibrous sheath of the worm being exposed, the superior surface is incised longitudinally and a small strabismus hook inserted inside its interior. By these means the female *D. medinensis* is hooked out. The loop of the worm is held tightly in the fingers while intermittent traction and massage are again employed. Should it be impossible to liberate the distal end of the parasite, a second incision is made over another palpable segment of the worm, and both ends of the central loop are cut across and the intermediary portion removed. It is most important that the proximal head portion of the worm should be removed through the sinus, not drawn through the sheath in the subcutaneous tissues in the reverse direction, or otherwise there will be pollution with organisms from the mouth of the sinus (Fig. 181.)

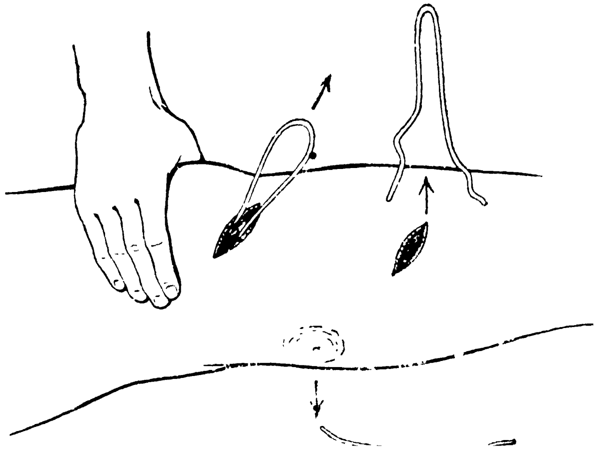


Fig. 181.—Diagram of removal of guinea-worm. (*After Fairley.*)

The latest and apparently the most efficacious treatment is by a dye, phenothiazine (Mountjoy Elliott, 1942). Finely powdered and triturated, it is emulsified with *adeps lanæ* and olive oil. A certain amount of heat is required to keep the solution sufficiently fluid to be drawn up into a hypodermic needle. Each injection consists of 10 c.c. of the emulsion, containing 1 grm. of phenothiazine. The site of the injection is anæsthetized by infiltration with novocaine. Three injections are usually made as near the course of the buried worm as possible. Usually, 4 grm. of phenothiazine is given in one treatment, and the site massaged for five minutes. Injections are made at weekly intervals and rarely more than two courses are needed. After 5 to 7 days the worm may be extracted by the rolling stick method. The rolling should be preceded by strong pressure with the fingers along the course of the worm tract in the direction of the sinus. This milking action should be performed for about 2 minutes. No toxic symptoms have been noticed.

Prophylaxis.—It is evident that prevention is merely a question of protecting drinking-water from pollution by guinea-worm patients. Leiper demonstrated that cyclops are killed by raising by a few degrees the temperature of the water in which they live. He suggested heating by a portable steam generator the water in wells and water-holes which are known to be sources of guinea-worm infection. Alcock found that the addition of a trace of potash to the water is equally effective. In Mysore, Moorthy found that step-wells are the greatest source of infection, especially in high-caste Hindu houses. When barbel fish (*Barbus puckelli, B. ticto, Rasbora donicornicus*), which feed voraciously on cyclops, are introduced, the guinea-worm disappears. Otherwise the wells must be treated every fourteen days with *perchloron* (bleaching-powder substitute).

CHAPTER XLIII

PARASITES OF THE LUNG AND LIVER

I. PARAGONIMIASIS (ENDEMIC HÆMOPTYSIS)

History.—This disease and the characteristic eggs appearing in the sputum of its subjects were described by Baelz and Manson in 1880. Ringer, in 1881, was the first to find the mature parasite, which was afterwards described by Cobbold under the name of *Distomum ringeri*; subsequently it was recognized to be closely related to the previously described *Paragonimus westermanii* of the tiger. The main features of its life-history and pathological bearings have been worked out since by Japanese observers. Closely allied species are found in the pig, dog, cat, otter, mink and ichneumon (*see* Appendix, p. 884).

Geographical distribution.—Paragonimiasis occurs in China, Japan, Korea, Formosa, the Philippines, Nigeria and the Cameroons. In many of the endemic districts a notable percentage of the population is affected. Paragonimiasis is found in wild animals in the United States, but so far no human infections have been discovered there. The spread of the disease takes place by eggs in the sputum, more usually in the fæces; this is specially the case in cats and other domestic animals.

Ætiology.—The fluke, *Paragonimus ringeri* (*westermanni*), is reddish-brown, thick and fleshy, oval, and measures 8–20 mm. by 5–9 mm. Development of the parasite proceeds in the fresh-water snail *Melania*, and thereafter the larva, or metacercaria, encysts in several species of fresh-water crabs (*Potamon*) and crayfish.

Man is infected by eating raw or improperly-cooked crabs, of which the Koreans are very fond, while the raw juice of crayfish is taken as a medicine for diarrhœa and whooping cough. The young parasites hatch in the ileum and in 24–42 hours penetrate the intestinal wall near the jejunum, reach the peritoneal cavity, and make their way to the diaphragm by penetrating the tendinous portion. Travelling beneath the pleura, the larvæ reach and pierce the parenchyma of the lungs, where cysts are found. In other organs they do not reach perfect growth (*see* Appendix, p. 885).

Pathology.—The lungs do not at first present any unusual appearances but, on looking closely, small brown spots are thickly distributed over the entire surface of the pleura and many tumour-like swellings of a deep red colour, in which the parasites are situated, can be seen. On making a section of the lungs, a larger or smaller number of what are known as "burrows" are discovered scattered about, particularly towards the periphery. These burrows consist of areas, somewhat larger than a filbert, of infiltrated lung tissue in which can be seen a number of tunnels filled with the same material that constitutes the characteristic brown sputum, which may also contain one or two trematodes. The septa between the tunnels may break down and a considerable cavity thus be produced; and as this occurs in connection with one of the bronchi, with which the tunnels always communicate, it may give the appearance of a dilated bronchus. One burrow may communicate with another. It is estimated that the number of eggs coughed up in twenty-four hours is over 13,000. Tubercle bacilli and paragonimus eggs are frequently found together.

When first discovered, it was supposed that *P. ringeri* was confined to the lungs, but it may affect the liver, peritoneum, testes, intestine, skin, muscle, and brain. It may cause intramuscular abscesses. In the brain it may form a tunnelled tumour similar to those in the lungs.

Musgrave, in his study of the pathology, pointed out that the peculiar bluish, cyst-like burrows of the parasite occur in many organs and tissues. Infiltration by the eggs produces, especially in serous membranes, little brownish-red patches sometimes visible to the naked eye. The intestinal mucosa is a common seat of infiltration, which gives rise to inflammatory reaction, ending in ulceration and the appearance of eggs in the fæces. The eggs may find their way into the spinal cord, as reported by Robertson, and produce transverse myelitis. At least 100 mature parasites have been found in a psoas abscess.

Symptoms.—The symptoms generally begin so insidiously that it is impossible to fix their onset with accuracy. The subjects of endemic hæmoptysis have a chronic cough and a vague feeling of distress in the chest, which is usually most urgent in the morning on rising. The fits of coughing expel a peculiar rusty-brown, pneumonic-like sputum, which can be produced at will almost at any time, and often in considerable quantity. In addition, the patient is liable to irregular attacks of hæmoptysis. Though usually induced by violent exertion, such attacks occasionally come on without apparent cause. The hæmoptysis may be trifling; on the other hand, it may be so profuse as to threaten life or at least to cause intense anæmia. Ogi stated that an outstanding physical sign in chronic cases is clubbed fingers. The physical examination of the chest is mainly negative. The patient is well-nourished. Resonance is usually normal, with a tendency to hyper-resonance, while râles can be demonstrated in a few instances.

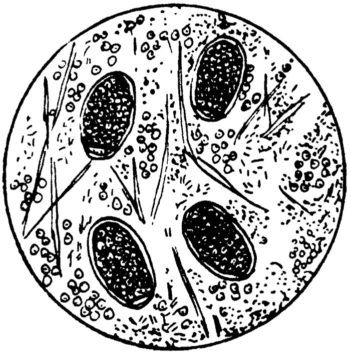


Fig. 182.—Eggs of *Paragonimus ringeri* in sputum.

The sputum.—Under the microscope the peculiar colour of the viscid, pneumonic-like sputum is found to be due partly to red blood-corpuscles, partly to a crowd of dark-brown, thick-shelled, operculated eggs (Fig. 182). Besides pus-corpuscles there are large numbers of eosinophil cells. Charcot-Leyden crystals are often present. The eggs vary a good deal in size and shape; they are all distinctly oval, have a yellow, smooth, double-outlined shell, and measure from 80 to 100 μ by 40 to 60 μ. If the sputum be shaken up in water, and the water be renewed from time to time, in the course of a month or six weeks—longer or shorter according to temperature—a ciliated miracidium is developed in each egg. When the mature egg is placed on a slide with slight pressure on the cover-glass, the operculum is forced back, and the miracidium immediately emerges and begins to swim about and gyrate in the water.

Abdominal symptoms in some cases may also be present; they consist of dull abdominal pains and occasional diarrhœa. The abdominal wall feels hard and is tender; at the same time symptoms of liver cirrhosis, appendicitis, enlargement of the prostate, epididymitis and adenitis may be present.

Cerebral symptoms.—When the disease affects the brain, especially in children, a peculiar form of Jacksonian epilepsy may be a feature for a considerable period, and may end in hemiplegia, aphasia, visual disturbances, homonymous hemianopia, pareses or monoplegias of various degrees.

Generalized.—In what is known as generalized paragonimiasis, in addition to the symptoms noted above, there is generalized lymphadenitis, especially affecting the axillary and inguinal groups, often associated with cutaneous ulcerations.

Diagnosis.—Diagnosis is at once established by the discovery of the characteristic eggs in the almost equally characteristic sputum. The sputum is sticky, not foamy, and resembles that of pneumonia. Charcot-Leyden crystals are usually present. Râles and other physical signs of lung consolidation are not usually discoverable. If the intestine or liver is implicated, eggs may appear in the stools.

One-sided convulsions or hemiplegic affections in a native of, or a visitor from the countries in which this trematode is endemic, should suggest examination of the sputum on the chance of discovering the parasite. Should eggs be found, there is a strong presumption that the cerebral trouble arises from a trematode tumour in the brain.

In the endemic zones of paragonimiasis, even in the absence of eggs in the sputum, Musgrave recommended that this parasite should be suspected in cases of chronic epididymitis, enlargement of the lymph-glands or prostate, liver cirrhosis, and skin ulceration. As some of these conditions are also found in *Bilharzia japonica* infection, the operculated eggs of paragonimus should be carefully distinguished from those of this parasite. The sputum should be examined bacteriologically to exclude the tubercle bacillus. Blood examination usually discloses a moderate leucocytosis of about 15,000 and there is usually no rise in the eosinophil cells.

The cutaneous ulcerations have to be distinguished from those of oriental sore.

Bercovitz reported that X-ray examinations of the lungs are very disappointing, while lipiodol infiltration shows no cavities, probably because the paragonimus burrows are situated at the periphery of the lung. Wang and Hsieh, on the other hand, described well-defined opacities and isolated infiltrations in various parts of the lung field.

Ando described a Bordet-Gengou complement-fixation test, using an extract of the body of the adult worm as antigen. This probably, when fully worked out, will constitute an efficient aid to diagnosis in obscure cases. From the clinical aspect paragonimiasis has to be distinguished from bronchiectasis more than any other condition.

Treatment.—So far no means of expelling the parasite from the lungs has been discovered. In cerebral paragonimiasis it might be possible by operation to remove the parasite and associated tumour, and thus afford a chance of recovery in a condition which has hitherto proved fatal. Kobayashi and Ando reported encouraging results with emetine, which is said to lessen the sexual activity of the trematodes. The drug is injected intramuscularly in doses of 1·25 c.c. of a 2 per cent. solution four times daily for five days, but it must be used with great caution, especially where there is any myocardial trouble. This was confirmed by Bercovitz, who gave emetine in 1 gr. daily doses for periods of seven days. To and Ko injected carpain subcutaneously, 5 per cent. in normal saline. The total quantities were 0·3 grm. over six days, and 1·1 grm. over 23 days. Bercovitz reported that marked improvement follows lipiodol injections into the bronchi. Yokogawa and Ro claimed encouraging results in experimentally infected dogs with intramuscular sulphanilamide (*prontosil*). Subsequently they treated nine cases of human paragonimiasis with intramuscular prontosil, 2·5 per cent. solution, giving a total of 60–165 c.c., simultaneously with intravenous emetine, 4 per cent., 12–23·5 c.c., over a period of seven to seventeen days. Degenerative changes were observed in eggs in the sputum after three days' treatment. Favourable signs were a decrease in the amount of sputum and disappearance of blood. It is claimed that this treatment proved successful in 50 per cent. of cases.

Prophylaxis in this, as in so many other animal-parasite diseases, lies principally in securing a pure water supply for drinking and bathing purposes, and avoiding all uncooked articles of diet, especially crabs and crayfish, which might be supposed to contain the young parasites. The sputum and fæces should be destroyed. In Chosen, Korea, an enlightened Government has waged a campaign against crabs, and has rendered their sale unlawful, while the populace is being educated about the dangers by means of posters and advertisements.

II. CLONORCHIASIS

Geographical distribution.—The trematode responsible for this disease has been found in many Eastern countries, including India, Mauritius, Japan, Korea, Formosa, China, and Tonquin. In South China, Faust and Khaw determined that the fish-raising industry is responsible for the high incidence in Kwantung Province. In Central Japan, according to Katsurada, there are certain districts in which it affects from 56 to 67 per cent. of the population, and Léger found the eggs in 50 per cent. of the natives of the East Coast of Indo-China. Recently, an endemic area has been discovered on the Pacific Coast of California, the infection having been imported by Chinese immigrants.

Ætiology.—The parasite, *Clonorchis sinensis*, measures 10 to 20 mm. by 2 to 5 mm.; it is oblong, narrow, flat, and somewhat pointed anteriorly, reddish, and nearly transparent. Development outside the human body takes place in two different intermediary hosts—primarily, a mollusc, *Bithynia*, usually *B. striatula*; and secondarily, several species of freshwater fish of the carp family. (For further details, *see* Appendix, p. 882.)

Pathology.—*C. sinensis* inhabits the bile-ducts. It thickens the walls of the biliary canals and expands them in places into cavities and diverticula as large as filberts, the walls of which are thickened with fibrous tissue. In these cavities vast numbers of parasites may be found. The diverticula communicate with the bile-ducts, along which the eggs of the parasites, and sometimes the parasites themselves, escape into the intestine. The affected liver is enlarged as a whole, although the tissue in the immediate neighbourhood of the diseased bile-ducts is atrophied. The spleen, also, may be hypertrophied and the intestine in a condition of chronic catarrh. This trematode is sometimes found in the pancreatic ducts, in the duodenum, and in the stomach, associated with ascites, and even with anasarca. According to Hoeppli it may produce carcinomatous changes, while Kown and his associates found new growths in the liver connected with this infection.

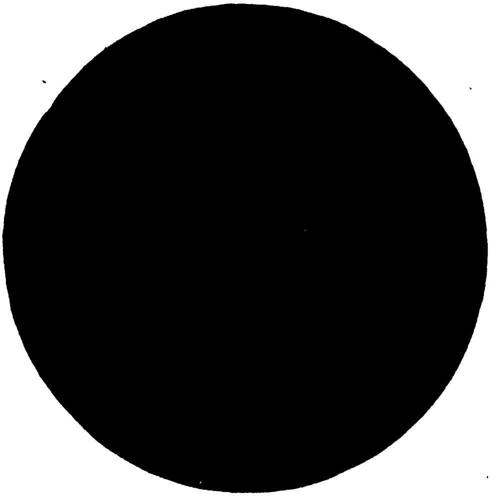


Fig. 183.—Eggs of *Clonorchis sinensis* in fæces. × 250.
(*Microphotograph by Dr. John Bell.*)

This parasite, which for long was supposed to be practically innocuous, is now held to be the cause of a serious cirrhosis of the liver, which may terminate fatally; indeed, there can be no doubt of this in view of the fact that several thousand parasites were present in some cases. Sambuc and Baujean counted 21,000 at one autopsy, and reckoned the total weight of the parasites at 300 grm.

Symptoms.—When the infection is severe the liver becomes enlarged, and chronic diarrhœa, with recurring attacks of jaundice, sets in. Late anasarca appears, and gradually a cachexia, resembling that of sheep-rot, is established, which, in the course of several years, may prove fatal. In lighter infections there is indigestion, epigastric distress and, sometimes, night-blindness (Bercovitz). The Editor investigated one case in which clonorchis infection appeared to be the cause of acute cholecystitis (strawberry gall-bladder).

Diagnosis.—It would be well to bear in mind this and other parasites in approaching the diagnosis of obscure hepatic disease associated with diarrhœa and jaundice in patients from the East. The discovery of the eggs (Fig. 183) in the stools should give correct diagnosis. Associated with this disease there is generally a leucocytosis of over 30,000 and eosinophilia of over 40 per cent. Toullec and Riou employed the duodenal sound, finding large numbers of eggs in the aspirated bile, even when they failed to demonstrate them in the stools.

Treatment.—The patient should be removed to a non-infected area and given nourishing food. Intravenous emetine has been found of little avail. Several observers (Haeck, Kinugasa and others) injected foüadin intravenously with some degree of success. In *vitro* experiments have shown that gentian violet, malachite green and Nile blue are lethal to clonorchis in a concentration of 1 in 40,000. The former dye appears to be most effective.

Faust found that, in experimental cats, gentian-violet *per os* causes death of the fluke after preliminary stimulation of ovulation. About 80 mg. per kilo weight was found to be the correct dosage. Unfortunately in this strength this drug appears to be toxic, though it opens up an important line of clinical research.

Continuous non-surgical bile drainage has been extensively practised in Korea by means of the duodenal tube. It is found necessary to cocainize the throat to prevent reflex vomiting. As a rule, it is possible to allow the tube to remain in position continuously for several days. During the day-time bile is collected every two hours, following stimulation by 50 per cent. magnesium sulphate through the tube. The bile is examined microscopically for clonorchis eggs, and the number per 4 cu.mm. counted. It is however, necessary to state that this procedure does not remove all the eggs, but it is useful in getting rid of toxic material, and the results are most spectacular when the liver is enlarged and tense. Bilary drainage is not always harmless, and is sometimes followed by shock.

Prophylaxis.—Manifestly, the Chinese habit of eating raw fish should be deprecated. The addition of vinegar does not kill off the clonorchis cysts. Animals and men harbouring the parasite should be prevented from fouling water, whether used for drinking, bathing, or agricultural purposes. The freshwater snails which serve as intermediary hosts inhabit the ponds in which edible fish are cultivated by the Chinese.

CHAPTER XLIV

INTESTINAL PARASITES

I. ASCARIASIS

Definition.—Infection of the alimentary tract with the roundworm, *Ascaris lumbricoides.* This worm is large and familiar; it may give rise to no special symptoms save inconvenience but may be the starting-point of severe complications. The worm and its life-history are described on p. 908.

Symptoms.—The normal situation of ascaris in the bowel is the jejunum. There, as can be shown by skiagraphy, the worms lie motionless, curled up in bundles, so that the bowel can be stuffed with worms like a well-filled sausage. The worms ingest the barium, and their situation is clearly shown by the opaque outline of the intestinal tract. Toxic symptoms are probably attributable to *ascaron,* a mixture of albumoses and peptones. Fülleborn and Kikuth studied the allergic phenomena of ascaris infection. These are well known. Some individuals manifest a peculiar sensibility to ascaris emanations, and entry to the laboratory where ascaris worms are being dissected is enough to cause conjunctivitis, urticaria, asthma, and even " fever." The skin of these people is extraordinarily sensitive to minimal doses of ascaris substance, and in a few minutes a red and extremely sensitive wheal is produced. The passage of a worm is attended by an intolerable itching at the anus and vomiting may cause œdema of the glottis. In children, ascaris infection may produce pallor of the face, with blue rings under the eyes and sometimes interference with nutrition; on the other hand, the infection may never be suspected until eggs are found in the stools.

In many instances the ascaris gives rise to no very noticeable symptom; in others it is credited with a number of ill-defined gastric and perhaps nervous troubles—capricious appetite, foul breath, restless sleep, peevishness, vague abdominal pains, nausea, and so forth. It may cause most pronounced urticaria. Sometimes the worms get into the stomach and are vomited, giving rise to no inconsiderable alarm. They may even creep up the œsophagus and into the mouth, or out by the nostrils, and cause suffocation by wandering into the rima glottidis. When aggregated into masses in the intestines they may cause volvulus, or even intestinal obstruction. They have been known to enter the pancreatic and bile ducts, giving rise to jaundice and abscess of the liver; to cause acute hæmorrhagic pancreatitis by blocking the bile duct; to penetrate the intestinal wall and escape into the peritoneum, causing peritonitis (in one Chinese quoted by Hsü, over 1,500 ascaris were removed from the peritoneal cavity); or to burrow into the abdominal walls and cause localized abscess. Eggs have been demonstrated in pearl-like nodules encysted in the peritoneum and mesentery. The worms may invade the lumen of the appendix, which may be packed with eggs, and cause appendicitis. In women, they may invade the generative tract, and have been found encysted in the Fallopian tubes. In children there is characteristically a protuberant abdomen ; normal digestion is disturbed ; there is loss of appetite and sometimes insomnia. The most common complaint is intermittent intestinal colic.

Although "ascaris pneumonia" is not often diagnosed it has often been suspected in West Indian negroes. In experimental animals heavily infected with ascaris larvæ, death takes place from pneumonia after four to five days. The larvæ, in their wanderings through the lung capillaries, must give rise to considerable disturbances. In North America pneumonia is much feared by some breeders of pigs, as the ascaris of the pig is very similar to, and has the same life-history as *Ascaris lumbricoides*. This ascaris is a definite biological species, as it cannot develop to maturity in man, nor can the reverse take place. Koino, a Japanese investigator, swallowed 2,000 ripe human ascaris eggs. Six days later he was attacked by definite pneumonia with dyspnœa, cyanosis, eosinophilia and pyrexia of 104° F. which lasted seven days. The syndrome of tropical eosinophilia seemed to be reproduced (*see* p. 675). The sputum was profuse from the eleventh to sixteenth days, and contained ascaris larvæ, of which 202 were counted. The liver was enlarged, there was congestion of the conjunctiva, and severe muscular spasms. After a period of fifty days from the time of infection, 667 ascaris, varying in length from 3–8 cm., were voided. It is said that during their migrations in the lung the larval worms may give rise to hæmoptysis.

It is estimated that each female ascaris in the bowel produces 2,000 eggs for every gramme of fæces.

Diagnosis.—It is well, when puzzled over some obscure dyspeptic condition in tropical patients, to bear the ascaris in mind. The stools ought to be examined with the microscope. Various concentration methods may be employed for demonstrating the eggs (*see* p. 1008). If they are found, a dose or two of santonin may clear up the diagnosis and cure the patient.

Ascaris infection is usually associated with an eosinophilia, but this is by no means so reliable as was formerly considered, and the Editor has seen heavy infections without any increase of these cells. During the invasion stage, when the larvæ are resident in the lungs, there is a very definite eosinophilia, but this diminishes as the worms enter the intestinal canal. In America, Jeller, Kaspari and Leathes found in European children an average eosinophilia of 9·9 per cent. and in negro children about 5·3 per cent.

The cutaneous reactions to *ascaris antigens* are of little practical importance and Fülleborn considered the "scratch test" with powdered ascaris more reliable than intradermal injection. In many infected individuals the test remains negative, and, moreover, a person who has once been infected and cured remains thereafter sensitive.

Skiagraphy can be employed in diagnosis. Films taken four to six hours after an opaque meal display ascaris as a cylindrical filling defect, or as a string-like shadow produced by opaque substance which the worm has swallowed. As a rule, the worms are arranged parallel to one another in bundles.

TREATMENT

The most widely employed drug for the treatment of ascaris is **santonin,** but it is by no means as effective as was formerly thought, and is apparently more lethal to female than to male worms, while it has been proved that even after several treatments the worms may not be completely eradicated. It is apparently effective to a limited extent when given in suppositories. The dose by the mouth is ½–1 gr. (0·032 to 0·065 grm.) for a child, and 3–5 gr. (0·194 to 0·324 grm.) for an adult. A good method is to prescribe three doses on successive nights, the first and the last dose followed by castor oil the next morning.

An alternative method consists of taking santonin, gr. 5, with calomel, gr. 2–3, on three successive nights followed by a saline purge, ℥ss of magnesium sulphate, two hours afterwards. As children in the tropics are more usually infested with ascaris than are adults, it is necessary to adapt the dosage to their age according to the generally accepted rules; it may be one quarter or one fifth of those stated.

Santonin, $C_{12}H_{18}O_3$, is a crystalline lactone obtained from santonica, which consists of the dried unexpanded capitula of *Artemesia cina*, Berg (Fam. *Compositæ*), a small undershrub which grows plentifully in Turkestan and is known as "Levant wormseed." It is almost insoluble in water, but soluble in 90 per cent. alcohol (1 in 44), chloroform (1 in 2·5) and castor oil (1 in 200). When exposed to sunlight it turns yellow. It does not kill the worm, but probably affects its vitality, causing it to migrate to the lower bowel. The dose is best prescribed with sugar and 3·5 gr. of calomel for an adult. It is more active in a mixture with castor oil such as:

℞	Santonin	gr.iv	(0·259 grm.)
	Ol. ricin.	ʒiii	(10·65 c.c.)
	Mucil. acac.	ʒiv	(14·21 c.c.)
	Syrup. simp. . . .	ʒi	(3·55 c.c.)
	Aq. menth. pip. . . .	℥iss	(42·63 c.c.)

This is taken after fasting in the morning.

The symptoms of santonin intoxication are a green or yellow urine, if acid, purplish or red if alkaline. It may cause yellow vision, headache, vertigo, nausea, and even epileptiform convulsions, and it may produce irritation of the kidneys, with painful micturition and hæmaturia.

Oil of chenopodium (*see* p. 770) is sometimes more effective than santonin. It may be given in a mixture with liquid paraffin (one ounce) or in capsules. The maximum adult dose is 24 minims (1·421 c.c.), and is usually given in two portions of 12 minims each within a quarter of an hour. Capsules of oil of chenopodium usually contain three minims each of the drug. Eight of these should be given early in the morning, in two portions of four capsules each.

Carbon tetrachloride (tetraform) is given as for ancylostomiasis, with the same precautions (*see* p. 770). It is given alone, in capsules, in syrup, or with liquid paraffin in doses of one drachm for an adult and proportionately less for children. It should be preceded the night before and followed by a dose of salts such as half an ounce of magnesium sulphate.

Combined treatment, oil of chenopodium together with carbon tetrachloride, is the most efficacious in the Editor's opinion. They may be given together in a mixture, as in ancylostomiasis, but it is probably best to give the carbon tetrachloride on one day, and the oil of chenopodium on the following. The worms, when expelled, are always dead and sometimes disintegrated. It is important to warn the patient that they may not appear in the dejecta for two, or even three days, after completion of the treatment. Fatalities from carbon tetrachloride treatment have been reported. In ascaris cases they may be due to blockage of the bowel or of the bile-ducts by masses of dead worms.

Hexylresorcinol.—In America this drug has recently come into favour as a vermifuge for ascaris. Crystals in gelatin capsules or sugar-coated pills are given by the mouth in doses varying from 0·1 to 1 grm. three times daily, according to the age of the patient (0·1 grm. for each year up to ten). The drug should be given on an empty stomach and should be followed by a saline purge.

Prophylaxis.—The prophylaxiasis of ascaris is essentially one of efficient sanitation, and the same principles apply as in ancylostomiasis. Vegetables grown by native gardeners who use night soil as manure form an important source of infection. *Eimeran*, a coal-tar preparation containing organically combined sulphur, has been found effective in killing off ascaris eggs, and is useful for latrines in the tropics. Ascaris prevalence constitutes the most sensitive measure of efficient sanitation. Only when 100 per cent. of the population use latrines regularly can any appreciable effect on the amount of ascaris infection be observed.

Phenothiazine (thio-diphenyl-amine) a thiazine dye, which has been widely employed in veterinary medicine, kills the ascarides, which are stained red by the drug. The dye is mostly excreted in the urine, which is tinged red. The dose for an adult man is about 8 grm. and should be followed by a dose of sodium sulphate. Phenothiazine must not be exhibited to children in whom it may produce severe anæmia.

II. ANCYLOSTOMIASIS[1]

Synonyms. Uncinariasis; Hookworm Disease; Egyptian Chlorosis.

Definition.—A disease in its more pronounced forms characterized by great anæmia, debility, and cardiac incompetence, due to blood destruction by *Ancylostoma duodenale* and *Necator americanus*, nematodes which inhabit the small intestine, and may be present in enormous numbers. The ancylostome amounts to a positive curse in many tropical countries, on account of the dangerous cachexia—ancylostomiasis—to which it gives rise.

History.—The worm, now known as *Ancylostoma duodenale*, was first recognized by Dubini in 1838, and in 1843 he published a detailed account of it, but apparently did not recognize its pathogenic importance. Bilharz (1853) and Griesinger (1854) connected the parasite with the extremely severe chlorosis prevalent in Egypt, but it was not until the very fatal epidemic of anæmia among the miners in the St. Gothard Tunnel (in 1880) had called the attention of European observers to the subject that the importance of this parasite as a pathogenic agent began to be properly apprehended.

Geographical distribution.—The ancylostome has been found so widely diffused that it may be said to occur in all tropical and subtropical countries. It occurs in Belgium, and was found by Haldane to be the cause of an epidemic of severe anæmia in a Cornish mine. In northern countries it is rare ; but it is abundantly present in the south of Europe, and in the tropical and subtropical regions of Asia and America. It is especially prevalent in Egypt, Siam, South China, and Malaya. In India, Ceylon, and the East Indies it is a source of grave disability in plantations, mines, etc. It occurs abundantly on most of the Pacific islands, and exists in North and South Queensland.

---

[1] A complete bibliography on this disease has been published in a volume by the Rockefeller Foundation International Health Board. Publication No. 11.

Ætiology (Fig. 184).—The normal habitat of *A. duodenale* is the small intestine of man, and particularly the jejunum ; less so the duodenum, rarely the ileum or lower reaches of the alimentary canal ; very occasionally, it is found in the stomach. In these situations it attaches itself by means of its powerful buccal armature to the mucous membrane, from the blood of which it obtains a plentiful supply of nourishment. It is supposed to shift its hold from time to time, the abandoned bite continuing to ooze blood for a short period. It is said to be very prodigal of the blood it imbibes, the red corpuscles passing through its alimentary canal unchanged, and the plasma alone being utilized.

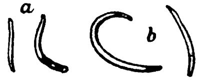


Fig. 184.—Ancylostoma duodenale.
Nat. size. (*Dubini.*)
a, Male ; *b*, female.

The male and female ancylostomes—present generally in the proportion of one of the former to three of the latter—do not differ so much in size as do many of the other nematodes. The male (Fig. 184, *a*) measures 8–11 mm. by 0·4–0·5 mm. ; the female (Fig. 184, *b*) 10–13 mm. by 0·6 mm.

Necator americanus closely resembles *A. duodenale*, but is shorter and more slender (*see* Appendix, p. 912). At first it was thought to be confined to the American continent, but it has been found by Looss and others in pygmies from Central Africa, and by others again in Rhodesia, India, Ceylon, Fiji, the Philippines, and elsewhere. Near Darjeeling in India it is found as a pure infection (Lane), whilst in Egypt *A. duodenale* occurs alone.

The life history of these two parasites is identical.

Reproduction and mode of infection.—The female ancylostomes produce a prodigious and never-ending stream of eggs, which pass out in the fæces. In the body of the host the development of the embryo within the egg does not advance very far ; but on leaving the human host it proceeds, in suitable circumstances, so rapidly in the egg that in one or two days a rhabditiform embryo is hatched. This minute organism is very active, voraciously devouring what organic matter it can find and, for a week, grows rapidly and moults twice. After the second moulting it passes into a torpid condition, in which it ceases to eat, and growth is suspended. In this state it may live for weeks or months, moving about more or less languidly in mud, or in damp earth, but it is rapidly killed by drying. It is said that it may also enter drops of dew on blades of grass. Cort and others demonstrated that the larvæ lose their sheaths while living in the soil, and continue to exist unsheathed. Arrived in its final host, after moulting again at the end of five weeks, it acquires sexual characters and the permanent adult form.

Infection is aided by indiscriminate defæcation, moist loamy soil, adequate shade and bare feet. There is special danger in badly-used or badly-constructed latrines and infected soils in plantations and gardens.

Looss demonstrated that the larvæ reach the intestinal canal by boring their way through the skin. From the subcutaneous tissue they enter the blood-vessels and lymphatics, and by this channel are passively transferred to the lungs. Here they leave the capillaries, enter the air-vesicles, and thence along the bronchi and trachea pass into the œsophagus, and so to the stomach.

The duration of the life of *A. duodenale* in the intestine has not been determined; some state it in months, others in years (Sonsino)—one to three. On account of liability to reinfection, this point—an important one in prognosis—is difficult to determine.

The exact number of ancylostomes necessary to produce symptoms has exercised much attention. Some consider that 100 are necessary to produce pathogenic effects and that 500 to 1,000 worms must be present for at least six months to produce well-marked hookworm disease. Others believe that very few ancylostomes, ten or so, may affect the general health and working powers.

According to Lane, the egg-laying capacity of a single female ancylostome is about 30 eggs per c.c. content of fæces per diem. Sweet, as the result of his studies in Ceylon, concluded that the average Cingalese has an intensity rate of hookworm infection of 2,200 eggs per grm. " basis-formed fæces," or as representing approximately one hundred ancylostomes. It is estimated that 53 per cent. of people have what is classified as" hookworm disease," the remainder being merely " carriers of worms."

In four persons from whom the worms were recovered, the average egg-output per day for each female worm was 28,080. Relatively it appears that the egg-count falls as the worm-count rises.

Pathology.—The exact rôle of the ancylostome worm in the production of anæmia is by no means settled. The following theories have been put forward of the causation of anæmia:

(*a*) Chronic loss of blood.
(*b*) Absorption of specific toxin.
(*c*) External conditions, such as diet and general hygiene.
(*d*) The damaged gut may play a rôle through repeatedly renewed bacterial infection.

On the whole, evidence points to the dietetic factor as playing the chief part in the reaction of the human body to this infection. As already mentioned, the bodies of the victims of ancylostomiasis are not wasted; on the contrary, there is plenty of fat in the usual situations. The appearance of plumpness is further increased by a greater or lesser amount of general œdema. There may be effusions in one or more of the serous cavities. All the organs are anæmic. The heart is dilated and flabby, its muscular tissue being in a state of pronounced fatty degeneration. The liver also is fatty, and so are the kidneys.

If the post-mortem examination be made within an hour or two of death, the ancylostomes, in numbers ranging from a few dozens up to many hundreds, will be found still attached by their mouths to the mucous surfaces of the lower part of the duodenum, of the jejunum, and perhaps of the upper part of the ileum; but if the examination has been delayed for some hours the parasites will have loosed their hold, and are then found lying in the mucus coating the inner surface of the bowel. Many small extravasations of blood—some fresh, others of long standing—are seen in the mucous membrane, a minute wound in the centre of each extravasation representing the point at which a parasite had been attached. Sometimes, blood-filled cavities, as large as filberts, are found in the mucosa, each cavity enclosing one or two worms and, probably, communicating by means of a small hole with the interior of the intestine. Old extravasations are indicated by punctiform pigmentation. Vesiculations and thickening of the mucosa may be evidence of a greater or lesser degree of catarrh. Occasionally, streaks or large clots of blood are found in the lumen of the bowel. The hookworms are thought to inject toxins from their oral glands; they certainly secrete some anti-coagulant substance. The actual sucking of blood is the most important factor, added to the fact that the worms frequently move from spot to spot. The iron-grey colour of the worms is due to the deposition of hæmosiderin granules in their intestine; sometimes they are red from freshly imbibed blood.

In acute cases eosinophilia is high, but gradually diminishes. Achlorhydria is comparatively common. In the chronic form of the disease the Van den Bergh reaction is negative. The average red cell count is 2,900,000 per c.mm., and the hæmoglobin 37 per cent. (Haldane). The average diameter of the red cells is 7·44 μ with reticulocytes less than 1 per cent. The hæmoglobin deficiency is not really as gross as suggested, because there is considerable increase in blood volume and the reduction in total hæmoglobin is much less than that suggested by the percentage figure. The average total blood-volume is 79·5 c.c. per kg. body-weight (normal 85 c.c.); the average plasma volume in ancylostome anæmia is 62·6 c.c. per kg. (normal 50 c.c.), so that the diminution of the total blood-volume can be accounted for entirely by the diminution of the red blood-corpuscles. The blood-picture is therefore that of a secondary microcytic anæmia, which is to a great extent curable by iron therapy.

Microscopical examination of the liver and kidneys shows the presence, within the cells of the parenchyma, of grains of yellow pigment having the reactions of hæmosiderin. The bone marrow is hyperplastic: erythropoïesis being dominant.

Symptoms.—There may be dozens of ancylostomes in the intestine without any appreciable anæmia, or, indeed, symptoms of any description whatsoever. Grave symptoms are the exception. It is important, therefore, to avoid concluding that the ancylostome is the cause of every pathological condition with which it may chance to concur.

On the other hand, many inhabitants of tropical and subtropical countries are in a state of chronic starvation. Living on coarse, bulky, innutritious food, they are liable to dilatation of the stomach and dyspeptic troubles. Any additional cause of malnutrition, such as a swarm of ancylostomes and a daily though perhaps small loss of blood, may be sufficient to turn the scale against them. In those countries, as elsewhere, there are many who live just on the borderland between health and disease; to such the ancylostome may prove "the last straw that breaks the camel's back." It is evident that, as a complication of typhoid, of kidney disease, of dysentery, of malaria, in fact of any chronic or exhausting disease, the importance of this anæmia-producing parasite cannot be ignored.

The practitioner in the tropics, therefore, must be constantly on the look-out, in all cases of anæmia, dyspepsia and debilitated conditions generally, for the ancylostome. He must bear in mind that this parasite, if permitted to remain in the intestine for a length of time, may be the cause not only of remediable anæmia, but of irremediable anæmia-produced degenerations of various organs. On this account, also, its early recognition becomes a matter of the first importance. It has been pointed out by many observers that ancylostomiasis is the source of considerable surgical risk, not only in rendering the operative procedure more difficult, but also in retarding convalescence. It is also said to increase the risk of delayed chloroform poisoning. Whenever possible, anthelminthic treatment should be instituted before operation, especially laparotomy.

Further, ancylostomiasis is an important disease from the standpoint of the employer of native labour. The invaliding and inefficiency which it causes among coolies, not to mention the deaths, are often a serious financial matter to the planter and the mineowner. To them any wisely directed expense or trouble undertaken for the treatment and control of this helminthiasis will be abundantly repaid by the increased efficiency of the labourer.

The essential symptoms of ancylostomiasis are those of a progressive anæmia—an anæmia which is generally associated with dyspeptic trouble, but which, in uncomplicated cases, is not associated with wasting. If the progress of a case be unchecked, serous effusions and fatty degeneration of the heart ensue, and death may occur from syncope or from intercurrent complication. Œdema may be localized, or there may be general anasarca. Most commonly it is confined to the face or legs.

There is a decrease in the total plasma protein and plasma albumin, with increase of globulin. The albumin-globulin ratio is usually less than one. The œdema is due to reduction of colloidal osmotic pressure due to decrease of albumin, which, in turn, is the result of deficient absorption.

Ground itch or ancylostome dermatitis is usually the first symptom noted (*see* p. 775), but one of the earlier is pain or uneasiness in the epigastrium. This is generally increased by pressure, but for the time may be relieved by food. In some people it may produce an acute and ever-present epigastric pain, which closely resembles duodenal ulcer and may often be mistaken for it. The appetite, sometimes defective, is more often ravenous, though its gratification is apt to give rise to dyspeptic trouble of various kinds—to colic, to borborygmi, and perhaps to diarrhœa of imperfectly digested food. Constipation may be present in some instances, irregularity of the bowels in others. The taste may be perverted, some patients exhibiting and persistently gratifying an unnatural craving for such things as earth, mud, or lime—what is called *pica* or *geophagy*. The stools sometimes, though rarely, have a reddish-brown tinge from admixture of half-digested blood. Sometimes they may contain small flakes of blood-tinged mucus. Pure blood is seldom passed ; and an extensive hæmorrhage, unless there be concurrent colitis, is rare, although, *post mortem*, quantities may be found in the small intestine. In the quiescent period the occult blood test is positive. Fever of an irregular intermitting, or even a subcontinued type is common. On the other hand, the temperature may be constantly subnormal, or these conditions may alternate. After a longer or shorter time, symptoms of profound anæmia gradually disclose themselves. The mucous surfaces and the skin become pallid, the face is puffy, and the feet and ankles are swollen. All the subjective symptoms of a definite anæmia now become more and more apparent; there are lassitude, breathlessness, palpitations, tinnitus, vertigo, dimness of vision, mental apathy and depression and liability to syncope. The circulation is irritable, and hæmic bruits can be heard over the heart and larger blood-vessels. Ophthalmoscopic examination may reveal retinal hæmorrhages.

Some of these symptoms, were it not that with the advancing anæmia there is no loss of weight, might suggest the possibility of tuberculous or cancerous disease or Bright's disease. Though hæmocytometric estimates testify to a slow and steady fall in the blood corpuscles until the lowest limit compatible with life is reached, there is no true poikilocytosis as in idiopathic pernicious anæmia, no excessive leucocytosis as in leucocythæmia, and not necessarily any enlargement of lymphatic glands, liver, or spleen. There is generally a marked eosinophilia of about 7–14 per cent., though in rapidly fatal cases these cells tend to disappear. The depression in the hæmoglobin value of the corpuscles is considerably greater than the fall in their number.

The rate of progress is very different in different cases. In some, a high degree of anæmia, and even death, may result within a few weeks or months of the appearance of the first symptoms. Such rapid cases are rare; more frequently the disease is exceedingly chronic, ebbing and flowing, or slowly progressing, through a long series of years. Acute cases develop terminal diarrhœa with passage of much mucus and, occasionally, blood, and are apt to be mistaken for various forms of dysentery.

Should such serious ancylostomiasis occur before puberty, the growth and development are apt to be delayed and stunted (Fig. 185).

There appears to be some reason for the belief that after generations of exposure to this infection a certain degree of tolerance is attained.

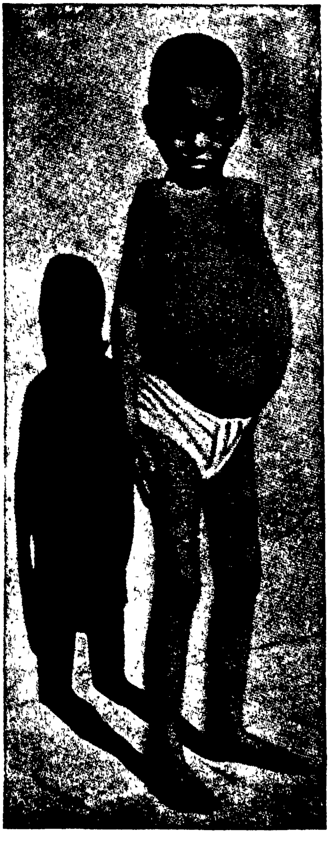


Fig. 185.—Ancylostomiasis in a South American Indian boy, showing stunted growth, characteristic facies, and protuberant abdomen. (*By permission of the Rockefeller Foundation.*)

It is not surprising that the severe nutritional changes associated with ancylostomiasis affect the mental powers of an afflicted population. Prolonged exposure in the European has led to the production of a race known as the "mean white," stunted both in mental and in physical capacity. In Jamaica, in districts where the whole population suffers from ancylostomiasis, not only are the people intensely indolent, but they are also predisposed, on this account it is said, to larceny and other crimes.

The practitioner in the tropics should always be on the look-out for subacute infections in Europeans on plantations and in mines. This does not apply solely to the men, but to their wives and children as well. Minor degrees of anæmia, an undue tendency to fatigue, lassitude and digestive disturbances are to be ascribed to this infection, even where, from the habits of the patients, it might not be suspected. In Europeans undoubtedly the infection may take place *via* the mouth and alimentary tract, but European children who are apt to play in sand, often used as a site for defæcation by natives, become infected in the usual way, *via* the skin.

Ancylostomiasis and pregnancy.—Wickramasriya found that hookworm disease exerts a deleterious influence on pregnancy, and that in heavily infected districts it is the most common cause of repeated abortions and miscarriage. Moreover, a heavy maternal and fœtal mortality is associated with it, and early interruptions of pregnancy and neonatal deaths are also included among its effects ; it is estimated that the combined fœtal and infantile mortality from this cause is almost 60 per cent. In the absence of skilled treatment, the chances of a successful pregnancy are remote if the hæmoglobin percentage has fallen below 60 at the commencement. Women who are heavily infected show a predisposition to toxæmias, such as pre-eclampsia and nephritic toxæmia.

Impaired renal function is an outstanding feature in the majority of expectant mothers suffering from ancylostomiasis. They must be regarded as persons with a lowered renal reserve who may enter into the stage of " decompensated impairment of renal function " with the onset of gestation. There exists great danger of death from post-partum shock, if the hæmoglobin percentage has fallen to 30 or under at the time of labour. Fisk found numbers of *A. duodenale* in the intestine of a child a month old who died of this infection.

Diagnosis.—Provided it is suspected, ancylostomiasis is easily diagnosed. In tropical countries, in patients coming from tropical countries, and in miners who work in very warm mines in cooler climates, anæmia with concurrent eosinophilia should always suggest a microscopical examination of the fæces (*see* Appendix, p. 1006). If the eggs of *A. duodenale* or of *N. americanus* are discovered, and no other reason for the anæmia is made out, the presumption is that one or the other of these parasites is responsible ; at all events, no harm is likely to result from treatment based on this supposition. On the other hand, if no eggs are found it must not be concluded that the case is not one of ancylostomiasis ; for sometimes, in the later stages of the disease, symptoms will persist although the parasites which caused them in the first instance have disappeared spontaneously, or have been got rid of by treatment. The usual method of diagnosis by microscopic examination of simple smears of stools does not convey a quantitative idea of the severity of the infection. The grade of infection runs from one to a thousand or more worms. Fæcal diagnosis has been rendered more accurate by the method of Clayton Lane, known as the flotation concentration technique (*see* pp. 916, 1008). In the majority of cases a test for occult blood in the fæces is positive, and Charcot-Leyden crystals are frequently found.

TREATMENT

General statement.—Several forms of treatment have been introduced for killing and expelling the ancylostome worms. These drugs necessarily contain a toxic principle, and considerable care should be exercised in their administration. Attention must be paid to details. The treatments will be placed in their chronological order.

I. Thymol ($C_6H_3(CH_3)\ (OH)C_3H_7I$) was introduced by Bozzolo in 1880. It is a phenol obtained from the oils of *Thymus vulgaris* (and other plants) and consists of large transparent crystals, slightly soluble in water and freely soluble in fats, oils, and alcohol. The amount of thymol absorbed depends upon the presence of these substances. If absorbed in excessive quantity, thymol may cause toxic effects, and death, preceded by a progressive fall in blood pressure. Some 30–40 per cent. of the absorbed thymol is excreted in the urine.

Dosage.—An adult man, 60 gr. of thymol ; an adult woman, 45 gr. ; in pregnancy, 30 gr. not to be given more than once a week. In advanced ancylostomiasis, with grave debility, it must be used with great caution.

Proportionate dosage.—For children under five, 8 gr. (0·51 grm.) ; 5–10 years, 15 gr. (0·97 grm.) ; 10–15 years, 30 gr. (1·943 grm.) ; 15–20 years, 45 gr. (2·915 grm.).

Thymol is best given in rice-paper cachets, in three doses of 20 gr. each, at intervals of an hour. Before its administration the patient should be put on liquid diet for a day, and have the bowels well cleared out by a saline aperient. It should be given on an empty stomach. If the bowels do not open spontaneously within four or five hours of the last dose, an aperient should be given. Usually, many ancylostomes are expelled and may be found in the motions. One such course of thymol may suffice ; but it is well, after a week has elapsed, again to examine the stools microscopically, and, if it be found that eggs are still being passed, to repeat the course of thymol once, or oftener.

Certain precautions have to be observed in employing this drug. In some cases, after the exhibition of thymol, the urine on standing becomes dusky, almost black, and reduces Fehling on prolonged boiling ; this is probably due to hydroquinone. At times it gives rise to a very unpleasant form of intoxication with vertigo and excitement. It is advisable, therefore, for the patient, while taking the drug, to keep his bed, and to lie down for several hours after the last dose. Thymol is very insoluble in water, and is consequently, in ordinary circumstances, not readily absorbed in poisonous quantities ; should, however, the patient, while thymol is present in the stomach, partake of any alcoholic drink, there is considerable risk of his being poisoned. Alcohol, ether, glycerin, turpentine, chloroform and oils are all solvents of thymol, and must therefore be avoided when this drug is being exhibited.

The treatment of thymol poisoning consists of washing out the stomach with warm water and of giving emollients to prevent or reduce corrosion. Stimulants, such as atropine, strychnine, digitalis or strong coffee, are useful in overcoming the depression of the respiratory and circulatory symptoms. Artificial respiration may have to be resorted to.

Without careful preparation by rest and judicious feeding, thymol must on no account be used in advanced cases of ancylostomiasis, or where prostration is extreme. It is contra-indicated in gastritis, dysentery, nephritis and active heart disease.

II. **Beta-naphthol** ($C_{10}H_7OH$) is given in much the same manner as thymol. The dose is 3–10 gr. (0·2–0·65 grm.). It is slightly soluble in cold water (1 in 1000), more soluble in boiling water in a dilution of 1 in 75 ; readily soluble in alcohol, olive oil and ether. In ordinary anthelmintic doses it produces hardly any noticeable symptoms, but in bigger doses it exerts an irritative action on the kidneys and may give rise to acute inflammation. The maximum tolerated dose is 40 gr. (2·59 grm.).

III. **Oil of chenopodium** (*Chenopodium anthelminticum* = goose-foot, wormseed, "Jerusalem Oak "). The active principle against ancylostomes or ascarides is *ascaridole* (45–70 per cent.), $C_{10}H_{16}O_2$, which is unstable, but which in 1 in 10,000 of oil kills the worms. It has a sharp, burning, nauseating taste, and is put up in hard gelatin capsules. The absorption of this substance is very rapid, and in toxic doses it causes depression of the respiratory centres. Excretion of ascaridole takes place mainly through the lungs. It is to be used with caution in cases with cardiac, hepatic, or visual disorders, and is definitely contra-indicated in pregnancy, nephritis, organic heart disease, hepatic dysfunction and intestinal ulceration. The maximum dose which can be given with safety is 3 c.c. in three gelatin capsules of 1 c.c. each at intervals of one hour. It is well tolerated by healthy individuals in hospital. For routine the dose is 1·5 c.c. (24 min.) in capsules containing 3 minims (0·177 c.c.) each. Eight of these capsules should be given—in two lots of four capsules at an interval of half an hour. For children, the dose should be 1 min. for each year of age up to 16. The drug should be administered three hours after a light meal. A quarter of an hour after it a strong saline purge (sodii sulph. ½ oz.) is given, with the object not only of washing the unabsorbed portion of the drug out of the intestine, but also of expelling the partially paralysed worms. Some prefer castor oil, but others consider that it tends to increase the absorption and add to the toxicity. A repetition of oil of chenopodium treatment should not be undertaken in less than a week.

Probably oil of chenopodium is more effective against *Necator americanus* than against *A. duodenale.*

IV. **Carbon tetrachloride** (CCl_4—*tetrachlormethane, tetraform*), a drug closely allied to chloroform, was originally introduced by Hall as a vermifuge and has been found suitable for the mass treatment of ancylostomiasis.

It is used as a solvent in rubber, chemical, pharmaceutical and paint industries, as a cleansing agent, as fire-extinguisher, insecticide sprays and soap solutions. It has also been used as a hair shampoo. It is a colourless, volatile, chloroform-like liquid with a pleasant quince-like odour and a specific gravity of 1·6. It is slightly soluble in water, and freely miscible in alcohol, oils, and other substances. When manufactured by direct chlorination of carbon bisulphide, it may contain traces of the latter drug. It exerts a preliminary burning effect on the mucous membrane, followed by anæsthetization. On exposure to light and air, carbon tetrachloride slowly oxidizes with the formation of poisonous substances, *phosgene* or *carbonyl chloride* ($COCl_2$), and it should therefore be kept in dark and tightly stoppered bottles. Absorption occurs from the stomach and intestines, but after large doses most of the drug is passed out in the fæces, combined with fats and fatty acids. Absorption in the body is by the lymphatic and portal routes, producing dizziness and drowsiness. Absorption may be followed by signs of liver damage ; jaundice may be seen on the second day after administration. Calcium chloride in full doses has a marked effect in controlling toxic symptoms. Acute carbon tetrachloride poisoning produces a board-like rigidity of the abdominal wall, and may resemble an acute abdomen, but the more usual signs are those of acute liver necrosis which may simulate yellow fever. Chronic poisoning resembles delayed chloroform poisoning with nephritis, oliguria, jaundice, vomiting and diarrhœa.

In ordinary anthelmintic doses the hepatic injury is not sufficient to produce noticeable effects, but toxic signs are specially noticeable when there is contamination with ethylene dichloride. Continued small doses may produce hepatic cirrhosis. Recent work indicates that the loss of ionized calcium and retention of guanidine are factors in the intoxication, interfering with normal metabolism. Guanidine accumulates in the blood. Indications are, therefore, for a diet rich in calcium and carbohydrates, though poor in fats and proteins. Alcohol must be avoided. Where any anxiety on behalf of the patient is aroused, glucose, one drachm, frequently by the mouth or in 5 per cent. intravenous injections, is indicated. It is also useful to administer calcium lactate in full (30 gr.) doses the day before treatment to increase the calcium content. Calcium chloride is useful in controlling symptoms. Rest in bed is not absolutely essential, though advisable in enfeebled persons. The after-symptoms are drowsiness, giddiness and headache. Toxic amblyopia has been recorded.

Carbon tetrachloride acts directly on the helminths and will remove 95–99 per cent. of all *Necator americanus* in a single treatment, but is less effective for *A. duodenale.*

The dose for an adult is 1 dr. (3·5 c.c.) taken in hard gelatin-coated capsules, each containing 30 min. (1·776 c.c.) of carbon tetrachloride ,after a partial fast of eighteen hours without preliminary purgation. A saline purge (sodii sulph., ½ oz.) is necessary 15–20 minutes after the drug, and an enema of hot water is usually required to empty the bowel. The treatment is best commenced at 8 a.m. and one-half of the total dose is taken after a quarter of an hour interval. The drug can be given to pregnant women, in whom oil of chenopodium is contraindicated. The minimal dose for children is 3 min. (0·2 c.c.) and it should be increased by that amount for each year of age up to maturity. Many clinicians find it pleasanter and safer to give the aperient together with carbon tetrachloride, 3 c.c., in castor oil, 15 c.c.

It is important to note that not all the dead ancylostome worms are found in the first stool passed ; they may continue to appear for three days after treatment. Similarly, the eggs of the parasite are held up in the folds of the intestinal mucosa and can be found in the fæces for at least a week after effective treatment has been completed.

Trichlorethylene ($CHCl : CCl_2$) in doses of one drachm (3·55 c.c.), which has a pleasanter taste and odour than carbon tetrachloride, is equally potent and safe, and is given the same way. On exposure to light, phosgene is apt to be generated, and this drug should always be stored in amber-tinted ampoules. If inhaled in an unrefined state, it acts as a lung irritant. The refined product trilene is used as an anæsthetic.

Tetrachlorethylene (C_2Cl_4) is soluble to the extent of 1 part in 10,000 of water. It is preferred to carbon tetrachloride by many, as having a pleasanter taste and being equally potent and safe. It has been given by Soper to adults in doses of 1·6 c.c. combined with 0·8 c.c. of oil of chenopodium. Maplestone gives 4 c.c. to men under 140 lbs. in weight. It may be given without excipient and may be mixed directly with a purgative, such as sodium sulphate. The dose for children is 2 c.c.

V. Combined treatment.—It is generally admitted that combined treatment with carbon tetrachloride and oil of chenopodium is more efficacious than the use of either drug alone. The two mix readily. The dose recommended is 2 c.c. (min. 34) of carbon tetrachloride with 1 c.c. (min. 17) of oil of chenopodium made up to 28·42 c.c. (one fluid ounce) in liquid paraffin. The same precautions being taken, it may be given in one dose or in two halves. Carbon tetrachloride and oil of chenopodium treatment can also be given on two consecutive days. Sodium sulphate, ½ oz. in a tumblerful of water, should be taken one hour afterwards. *Bedermin* is a preparation which conveniently contains both oil of chenopodium and carbon tetrachloride.

The following is a practical and easily tolerated method of administering both drugs:

(1) Starve overnight.
(2) 8.30 A.M.: 2 capsules (gelatin) of oil of chenopodium of 7·5 mins. each.
(3) 8.45 A.M.: carbon tetrachloride, 40 mins. (Four capsules of 10 mins. each.)
(4) 9.0 A.M.: mag. sulph. 4 drachms in water. Stools should become liquid within four to sixteen hours. If not, mag. sulph. must be repeated.

Ancylostome eggs may be passed in the fæces for six days after effective treatment. If they persist beyond this period, the course should be repeated.

It is hardly possible to get natives into hospital for treatment, so that systems of treatment to be completed at one sitting may have to be devised, e.g., the anthelmintic may be followed in half an hour or so by a dose of salts.

VI. Hexylresorcinol, 1 : 3 dihydroxy-4-hexylbenzol, is a white, waxy, crystalline substance, sparingly soluble in water, but exceedingly so in alcohol or vegetable oils. Introduced as an anthelmintic by Lawson, Ward and Brown, it is given in hard gelatin capsules or crystoids.

Give a light evening meal consisting of soft foods only, and the following morning give the dose *on an empty stomach*. The dosage for adults and children over twelve years of age is 5 pills; for children of eight to twelve years, 4 pills; six to eight years, 3 pills; under six years, 2 pills, 0·2 grm (3 gr.) each, with a glass of water. No food of any kind should be taken for at least four hours after treatment. Water may be taken freely, but alcohol is definitely contra-indicated. The patient may go about his usual occupation immediately after treatment and eat what he likes at the end of four or five hours. A saline purge should be given twenty-four hours after treatment to remove the dead worms. The patient may continue to pass worms for as long as ten days or two weeks after this single dose. If instructions as to food are carefully followed, one dose is usually sufficient.

Re-treatment is sometimes necessary because of re-infection, or because the patient has not followed instructions about food. Treatment should only be repeated after two weeks, if eggs are still present in the fæces. Unlike most anthelmintics, this product will successfully eliminate roundworms (*Ascaris lumbricoides*), hookworms and possibly also threadworms.

In crystoids the crystalline hexylresorcinol is gelatin-covered. If the gelatin covering becomes broken the drug may cause irritation to oral and œsophageal tissues. To avoid this, the crystoids *must be swallowed whole* with a glass of water; under no circumstances must the patient crush or chew them.

VII. Oil of eucalyptus, 30 min. (1·77 c.c.), chloroform, 45 min. (2.66 c.c.), and castor oil, 10 dr. (35·5 c.c.), one-half first thing in the morning, the other half thirty minutes later, was first employed by Manson as an efficient vermifuge in ancylostomiasis. It can be repeated for several days in succession, and can be used with advantage as an alternative to other treatments.

Convalescence.—The dieting of convalescents from serious ancylostome disease must, for a time, be very carefully conducted. A rich, full dietary is to be avoided until the powers of digestion have become re-established; otherwise, enteritis and diarrhœa may prove very troublesome and retard recovery. The anæmia responds to large doses of iron—ferrous sulphate—in doses of 24–36 gr. daily for three weeks, or even longer. Azmy and Zanaty recommend small blood transfusions, 200–300 c.c., which induce an increase of polymorphonuclear leucocytes and red blood corpuscles.

In cases of severe anæmia it may be wise to give a preliminary course of iron, with a generous and balanced diet, before administering the anthelmintic; in these cases full doses of carbon tetrachloride should be given with caution; it may be better to give a dose well below the toxic level and to repeat it as the patient becomes stronger.

Prophylaxis.—In devising a system of prophylaxis for ancylostomiasis, the fact that it is by means of the fæces of the already infected that the parasite is spread must be kept prominently in view. Fæcal contamination of the soil and water must therefore be prevented. The promiscuous deposition of fæces about huts, villages, and fields must be interdicted. Tea, coffee, cocoa, banana, rubber and citrus plantations, by reason of the intensive cultivation required, are potent sources of infection. Abundant and easily accessible latrine accommodation must be provided in coolie lines, in miners' camps, in native villages, and along the highways of traffic. The Chinese plan of storing night-soil for months in large, cemented, water-tight pits is a good one. It is known that, if the eggs of the ancylostome are kept in pure fæces, the embryo is developed and escapes from the eggs in due course; but it is also known that unless the larva be supplied with a certain amount of air and earth it soon dies. The thing to be avoided, therefore, is the mixing of *fresh* fæces with earth. Conditions of warmth, moisture and shade favour infection, but the infective stages of ancylostome larvæ are killed in a few minutes by direct sunlight. By the Chinese system the embryos of the ancylostome larvæ are killed and, at the same time, a valuable fertilizer is secured for the agriculturist. The presence of standing water is an advantage as it dilutes the bacterial food of the larvæ and they cannot feed in water. A rise in temperature increases activity of the larvæ, which use up the food reserves, so that in the tropics they rarely survive longer than six to eight weeks.

It is manifest that, in devising privies and sanitary regulations, the habits of the people they are intended to benefit must be taken into account; if native habits and prejudices are ignored, any system, no matter how perfect it may be in theory, will fail in practice. In America, intensive mass treatment after the installation of satisfactory latrines has been found most effective. The provision of a fool-proof latrine for natives is the chief difficulty. So far the " bored-hole " latrine, 16 ins. in diameter, has proved most acceptable. This is deep enough to prevent migration of hookworm larvæ, produces no odour and does not encourage fly breeding, but it must have a concrete or pressed steel squatting plate.

The water supply should also be carefully guarded from all possible sources of fæcal contamination. Drinking-water, unless above suspicion, should be boiled or strained. So far as possible, facilities for removing all earth and mud from the hands and dishes before food is taken should also be provided and their use encouraged. Badly contaminated ground had better be abandoned. The systematic periodical inspection of plantation coolies is recommended. At these inspections all subjects of anæmia or dyspepsia should be put aside for more careful examination ; if the eggs of ancylostomes are found in their fæces, a judicious dosing with some of the drugs mentioned may avert serious disease in the individual, and also prevent him from becoming a source of danger to his companions.

Until a few years ago, efforts at the prevention of ancylostomiasis were directed towards treating the surface of the soil, but recent work has shown that the ancylostome larvæ spend a considerable part of their life in the deeper layers.

Therefore a most important factor underlying efficient prophylaxis of ancylostomiasis in a community is the life-span of the infective larva during its existence in a free state in the soil. Practical experience gained by the directing authorities in the " hookworm campaign " suggests that this is much longer than experimental evidence indicates. According to Cort, Augustine and Payne, the life of the infective larva under these conditions does not exceed six weeks, and during that time it does not wander outside a 4-in. radius in a lateral direction, but can migrate to the surface from a depth of 36 in. Baermann showed that the larvæ may be recovered with ease from soil thought to be infective ; the technique consists in placing the suspected soil in a receptacle, together with a quantity of water ; the larvæ then rapidly migrate into the fluid, where they can be found and recognized.

Education of children in schools by means of diagrams and instructional films plays an important part in health propaganda in the United States. In South America it is noted that, although children wear shoes at school, where the chance of infection is not great, they commonly run barefoot at home, where infection is likely to be acquired. Nicholls recommended common salt as a prophylactic agent of some potency. It has the advantages of being cheap and, as a rule, easily obtainable. It has an injurious effect upon the larvæ, but requires to be brought into very intimate contact ; mere sprinkling is futile. Solid salt, however, when sprinkled on fæces, does not penetrate the mass for forty-eight hours.

In view of the great danger to health that exists in certain countries from this and similar parasites, the sanitary authorities in such places ought to circulate among the people, by means of printed leaflets or posters, a few simple directions for the prevention of ancylostomiasis.

Clayton Lane estimated that out of 315 million inhabitants of British

India, 45 million wage-earners were subjects of ancylostomiasis. Employers of labour in the Darjeeling district computed that the labourer's earning capacity when freed from this disease is increased by 25–50 per cent.

An energetic and many-sided campaign against the hookworm was waged in the United States, Asia, and Africa, financed by Mr. Rockefeller. State and county dispensaries for free examination and treatment of applicants were established. The total number treated in 11 States in 1912 was 238,755. A commission worked for a number of years, and treated 393,556 people at a cost of a little over a dollar per head. The reports issued by the Commission contain most valuable statistics, of which a few may be quoted. In Panama, in 1916, 30,094 persons were examined, and 80·4 per cent. found infected ; of these, 98·2 per cent. received treatment and 49·9 per cent. were cured. In Antigua, of the total population, 98·8 per cent. were examined, and 29·8 per cent. found to be infected ; treatment was given to 92 per cent. of the infected people, and 96 per cent. of these were cured. In British Guiana, out of 3,900 infected natives, only 8·6 per cent. remained as foci of infection at the end of the campaign. In Ceylon, of 4,567 tea-plantation coolies, no less than 95·6 per cent. were found infected. Nevertheless, unless constant preventive measures are maintained, mass treatment is not likely to be very successful in prevention. A few infected persons may soon re-infect a population, if the old bad habits are retained.

Darling thought that, as the agricultural and mining population within the tropics is so universally infected with hookworm, the detection of individual infections by microscopical examination was no longer necessary. The population should be treated *en masse* by an intensive method. The sanitarian should remember that an individual may be infected, yet not " affected " by the disease. Hence, apparently healthy persons constitute a danger to the community.

ANCYLOSTOME DERMATITIS

A form of dermatitis affecting the feet of coolies on plantations in Assam, in the West Indies, and probably elsewhere in the tropics, is ascribed to the penetration of the skin by ancylostome larvæ, and precedes by two to four months the generalized symptoms of ancylostomiasis. The disease is of much economic importance to the planter, and is variously known as ground itch, pani-ghao (Assam), water itch, water-pox, water sores, sore feet of coolies, cow itch (Queensland), sabañones (Venezuela), candelillas (Colombia), chauffie (Grenada) and mazamorra (Porto Rico).

The soil in the neighbourhood of coolie lines is extensively contaminated by fæcal matter. The bare feet of the coolies are constantly soiled with this larva-laden earth ; and in this way, in many tropical plantations, Looss's experiment is unintentionally carried out on a large scale. Dermatitis, vesiculation, and may be pustulation, or even extensive ulceration, and probably ancylostomiasis anæmia, ensue. A condition resembling larva migrans (*see* p. 804) is often produced by allied species *i.e. Ancylostoma braziliense* and *A. caninum* of the dog. The services of the affected coolie are lost to the planter until the irritation subsides and the anæmia is cured.

Fülleborn published the most complete account of this subject (1932). He pointed out that the ancylostome larvæ can only enter the skin when the soil conditions are favourable. They cannot enter through water alone, nor can they readily bore through the hard skin of the sole of the foot; they pass less easily through the tough skin of the negro than the soft epidermis of the European. It was shown by Khalil that the presence of a suitable host has no special attraction to the larvæ, but they are attracted by warmth (*thermotaxis*). The appearance of the skin lesions is dependent upon the number of invading larvæ. As Schüffner showed, the inboring larvæ first form a red point, and soon a small blister forms in which the larvæ can be demonstrated in sections, and the irritation of the skin is noted after some twenty minutes. Probably, the entrance of the larvæ also causes opportunities for the ingress of bacteria with formation of blebs and pustules, and this is the real "ground itch." It is by no means proven that ground itch is invariably ancylostome dermatitis, for it is not found in Egypt where this disease is rife.

Personal cleanliness and the use of some form of foot covering during the wet season, together with the prophylactic procedures for ancylostomiasis, are the special preventive measures indicated against this disease. Coolies working on irrigated land should be provided, if possible, with high, well-fitting boots. Antiseptic foot-baths and some soothing ointment are indicated. Treatment with drugs is best effected with strong salicylic solution in collodion or methyl alcohol. Barlow recommended 3 per cent. salicylic acid in ethyl alcohol.

III. CESTODIASIS

The tapeworms, *Tænia saginata* and *T. solium* and their cystic forms are common enough in the tropics and subtropics, their distribution being regulated by the presence or absence of their appropriate intermediary hosts—the ox in the one case, the pig in the other—and by the habits of the population in cooking and conservancy.

The broad tapeworm (*Diphyllobothrium latum*) occurs in Norway, Sweden, Russia, Turkestan, Japan (where the natives eat raw fish), Lake Michigan, Madagascar, and on the shores of Lake Ngami, South Africa.

The very severe degree of anæmia, referred to with almost wearying persistence in textbooks, is not seen in tropical practice in association with this parasite. Natural and experimental infections have been studied in which no blood-changes can be found.

The cestodes of man which have any claim to be regarded as special to warm climates are *Hymenolepis nana*, *Diphyllobothrium mansoni*, and *Spirometra mansonioides*.

TREATMENT OF TAPEWORM INFESTATIONS

General statement.—Preliminary starvation appears to be necessary for two days. On each of these sodii sulph. ½ oz., or castor oil ½ oz., should be given to clear out the bowel; the food should be restricted to weak tea, toast and unlimited amounts of lemonade and glucose D. A mixture to clear the bowel of mucus is useful, such as:

Ammon. chlor.	gr.xv	(0·972 grm.)
Tinct. limon.	♏xliv	(2·6 c.c.)
Spirit. chlorof.	♏x	(0·592 c.c.)
Aq. ad	℥ss	(14·21 c.c.)

I. Filix-mas treatment.—Filix-mas is the rhizome of the male fern ; it contains 5–8 per cent. of filicic acid (*filicin*), and a variable amount of aspidin ; both these substances are anthelmintics.

Extractum filicis liquidum, dose 45–90 min. (2·66–5·33 c.c.), has a disagreeable taste and is apt to cause vomiting, so the drug is best prescribed in gelatin capsules. When prescribed in draught, it is best given with *Mist. amygdalæ*, or with essential oils, *e.g.* cinnamon.

Haustus filicis maris consists of ext. filic. liq., 1 dr., syrup. zinzib., 1 dr., tinct. quillaia, ½ dr., aq. menth. pip. to one ounce.

Capsules contain 15 min. each of the liquid extract. The dose of these is one to six, according to the age of the patient. It is effective against *Tænia saginata*, *T. solium*, and especially against *D. latum*. The most difficult species to dislodge are *T. saginata* and *Hymenolepis nana*. On the morning of the treatment the patient should have a small cup of tea. For an adult man the full dose of filix mas is 1½ dr., for a female 1 dr. For specially resistant cases up to 120 minims (2 dr.) may be given with safety, as follows :—

8 a.m. : two capsules of 15 mins. of filix mas.
8.30 a.m. : repeat.
9 a.m. : repeat.

The patient must then lie perfectly quiet and take nothing but a few sips of water. At 10.30 a.m. half an ounce of sodii sulph. should be given. The bowels being opened freely by the salts, segments of the tapeworm should soon appear. All motions should be saved and strained to search for the head ; should this not be seen, a soap-and-water enema should immediately be given. Very often, however, the head is not found and it may be passed separately several days after the cessation of treatment ; therefore, failure to demonstrate the head does not necessarily indicate that the patient is not cured.

Some authorities reinforce this treatment with a mixture containing oil of turpentine, 20 min., emulsified with mucilage of acacia, or with a eucalyptus oil mixture containing 15 min. (0·88 c.c.) of eucalyptus.

The patient must rest in bed the whole day when undergoing treatment.

Oleoresin of aspidium (U.S.P.) contains *filicin*, the anhydride of filicic acid. To be successful the oleoresin should have been recently prepared. The patient should fast the day before treatment. At 6 p.m. on that day 30 gr. of mag. sulph. are given, and again on the morning of the treatment a similar dose. No breakfast should be taken, and after the bowels have been opened ½ oz. of the following emulsion is administered.

Oleoresin of aspidium	ʒi	(3·89 grm.)
Pulv. acac.	ʒss	(1·944 grm.)
Aq. dest. ad	℥i	(28·42 c.c.)

An hour later a second dose of ½ oz. is given and, after a further interval of two hours, a soap-and-water enema.

None of these treatments must be repeated oftener than once a month, otherwise toxic symptoms, such as polyneuritis and paralysis of the iris, may ensue.

The not uncommon practice of giving a second course within a few days of the first, in order to dislodge the head, is never successful.

Intraduodenal treatment of tapeworm.—Sawitzky recommends giving 30 grm. sod. sulph. in the afternoon, and starving the patient for the rest of the day. Next morning the bowels are opened by an enema, the patient swallows a catheter and is placed on his right side. The catheter enters the duodenum in 1–2 hours. He is then turned on his back, and a small glass funnel is attached. An emulsion of ethereal extract of male fern, 50 grm., gum arabic mucilage, 5 grm., sodium bicarbonate, 0·5 grm., distilled water, 50 c.c., is prepared. About three-quarters of this amount, equivalent to 3–4 grm. (50–60 min.) male fern, is introduced; immediately 50 c.c. (1¾ oz.) of warm 50 per cent. solution of sodium sulphate is poured in and the catheter extracted. Expulsion takes place in two hours.

II. Pelletierine.—Commercial pelletierine is a mixture of two alkaloids, pelletierine and isopelletieriene, and is obtained from the stem and root bark of the pomegranate (*Punica granatum*).

Pelletierine tannate, a mixture of the tannates of the alkaloids, is a light yellow powder, slightly soluble in water (1 in 700), but soluble in 90 per cent. alcohol (1 in 80). The dose is 7 gr. dissolved in alcohol, followed two hours later by castor oil, 1 oz.; a soap-and-water enema may be necessary.

Pomegranate bark is an infusion of the root bark of *Punica granatum*; 150 grm. is infused for twelve hours in a litre of water and then boiled down to half, and can be given by the mouth or be passed into the duodenum by Einhorn's tube. Before use the decoction is warmed to 100° F. and three doses of 65 c.c. (ʒ xviii) each are given at half-hour intervals, followed by a saline purge, after which the catheter is withdrawn.

III. Melon seeds.—These are obtained from *Curcubita maxima*, a native of the Levant. For medicinal use they should not be more than a month old and should be deprived of their seed-coats. They do not kill the tapeworm but, when followed by a saline purge, they do bring it away. The dose is 700 grm. for an adult, and the bruised seeds may be mixed with honey or milk, or with stewed fruit, and given on an empty stomach in the morning at 6 a.m. At 8 a.m. 3 oz. of *mist. alba* are given. This is the average dose for an adult.

IV. Areca nut.—Areca nut (*Areca catechu*) is used in China. The dose is 30 grm. of powdered betel, boiled for thirty minutes in 200 c.c. of water and taken on an empty stomach.

V. Sostol, a soluble yellow crystalline powder, is the hydrochloride of an acridine compound, and is said to be specially efficacious in diphyllobothrium and hymenolepis infections. The usual preparation is required. Sostol pellets are given early in the morning on an empty stomach, and adults receive 6 pellets of 0·1 grm. (1½ gr.), followed three hours afterwards by castor oil or a saline aperient. Children up to four years of age should take 1–2 pellets and children of from five to eight, 4 pellets.

VI. Carbon tetrachloride and oil of chenopodium.—Carbon tetrachloride anæsthetizes tapeworms and, especially when combined with oil of chenopodium, aids in their expulsion. It is combined in the following mixture.

Carbon. tetrachlor. . . .	ʒi	(3·5 c.c.)
Ol. chenopod.	♏xv	(0·88 c.c.)
Paraff. liq.	℥i	(28·42 c.c.)

This should be given in two doses, as in ancylostomiasis. Adults should receive the full dose ; children under six, 2 dr. ; up to eight, 3 dr. ; up to fourteen, 4 dr. The mixture should be made up fresh daily. Half an hour afterwards the patient should be given a saline aperient, or *Pulv. jalap. co.* 1–2 dr. (3·55–7 c.c.) may be used.

Hiyeda and Tarada discovered an active preparation in *raigan*—a mushroom (*Omphalia lapidescens*). This is given in a powdered state, in doses of 20 gr. three times daily for three days, without any preliminary preparation.

Gentian violet has been used to expel *Hymenolepis nana*. Cusso, or Kusso, a decoction made from the flowers of *Brayera anthelmintica*, is said to be efficacious in Abyssinia (p. 835) for removing *T. saginata*.

IV. CYSTICERCOSIS

Though the cysticercus, or bladder-worm stage of *Tænia solium*, normally develops in the pig, and infection of man takes place by eating pork, which contains the larval *cysticerci*, yet occasionally man himself may serve as intermediate host through accidental ingestion of the eggs of *T. solium*. The embryos may migrate to almost any organ, especially the muscles of the limbs, tongue, neck, or ribs and sometimes the lungs, liver, or heart, and they have been removed from the eye. One of the most striking recent contributions to medicine has been the demonstration by MacArthur that the embryos show a peculiar predilection for the brain. It has been known for some time that individual cases of cysticercosis may be accompanied by epileptic seizures. Investigations on epilepsy in young and otherwise healthy British soldiers, with good antecedents, has shown that cysticercosis is the cause. In one batch of 22 cases investigated by MacArthur 10 were proved to suffer from cysticercosis. In another 82 cases in British soldiers, who had served in India, evidence of infection with *Tænia solium* was obtained in 22. Indigenous cysticercosis in England has been recorded.

In some instances the fits commence about the time the cysts are first detected ; in others there may be a quiescent period of some years between the appearance of the cysts and the first epileptic seizure, or, in other instances, the cysts may become palpable after the onset of epileptic fits. The number of palpable cysts varies widely in different cases. Large ones which have been under observation for years may vanish in a few days. The bigger cysts usually contain dead larvæ and the cyst capsule is tense, owing to the large amount of contained fluid. The death of the larva is in some way associated with an increase of this fluid.

Pathology.—In the brain the cysticercus becomes enclosed by a wall of neuroglia ; small round cells and a few plasma cells are present between the delimiting neuroglia and the surrounding normal brain tissue, but later the tissues surrounding dead and disintegrating cysticerci undergo active degenerative changes with a marked cellular response. To the naked eye the degenerating tissues may be visible around the cysticercus as a discoloured ring, and later, if the patient survives, they undergo necrosis. This dead area, which may extend 5 mm. beyond the cyst, is ringed off from the normal brain by a wall of sclerosed neuroglia. (Fig. 186.)

After a variable period, determined in part by the resistance of the host, the parasites die and often undergo calcareous change. Calcification commences in the scolex, while the cyst capsule and its contents are unaffected. Calcification may stop at this point, and the cyst-wall may collapse through the escape of the fluid, or the collapsed cyst may be flattened out by pressure of the surrounding muscles and calcify in an extended form. Apparently, three years elapse between death of the cysticercus and calcification in the tissues, but cysts in the brain take longer.

Symptoms.—The fits may resemble the Jacksonian type, with cyanosis, biting of tongue and involuntary passage of urine. In some instances they are irregular, and cerebral tumours may be suspected. Nervous symptoms other than fits may be produced; thus the initial clinical picture may be that of disseminated sclerosis or cerebral tumour. Psychical states may supervene with cerebral irritability and loss of memory.

Usually, the invasion of cysticerci gives rise to no general reaction, but the patient notices the gradual development of small subcutaneous or intramuscular swellings. More rarely, a general toxæmia with pyrexia develops. Sometimes, too, the localized intramuscular swellings resemble a muscular dystrophy. Cysts may be present in large numbers without the patient's knowledge until they are discovered accidentally by radiological examination. As a rule, there is no ascertainable history of tapeworm infection; though in one case the first fits commenced during treatment in hospital for *T. solium*. There may be a history of incomplete fits, often regarded as hysterical, and every degree from petit mal to Jacksonian epilepsy. Intense headache may be the one symptom preceding a fatal attack. Psychical disturbances, melancholia, or acute mania may dominate the picture.

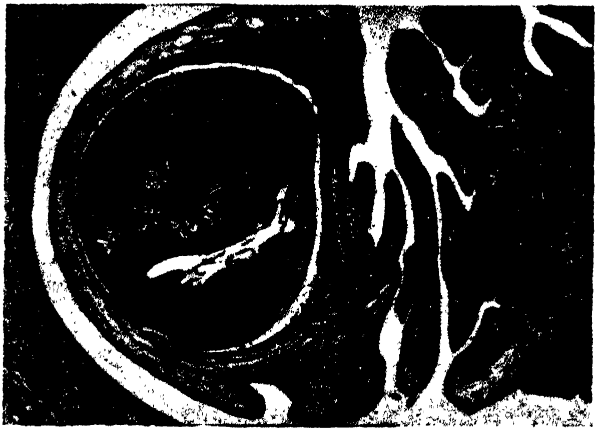


Fig. 186. Section of cysticercus from brain. (*Dr. Carnegie Dixon and Dr. J. D. Willis, Lancet,* 1941.)

Apparently no prophecy can be made of the duration of the epileptic symptoms Sometimes the seizures cease without apparent cause; in others they persist for eight years or longer. There have been several fatal cases in which the cysts have been found limited to the brain.

Diagnosis.—The most helpful sign in diagnosis is the development of palpable cysts in the tissues, and these may number from one to thirty or more. They may be the size of a hard pea, a hazel-nut, or even a pigeon's egg. Their situation varies widely; they have been found in the lips, masseter muscles, neck, chest, abdominal walls, back and groin, and if not numerous they are easily overlooked. Indeed, unless evidence of cysticercosis is systematically sought, diagnosis may be missed, as nodules may be absent at the time of examination, only to come out in crops at a later date. The radiological evidence may not be convincing for some years, as calcification does not usually take place for four or five years after infestation. Whilst they are alive the body is relatively tolerant, though they become active irritants when dead and calcified.

To demonstrate cysticerci, a suitable cyst is excised under local anæsthesia and the host capsule is enucleated. The appearance of the translucent membrane with its central " milk spot " is characteristic. If alive, the parasite may evaginate the head and neck, or it may be induced to do so by immersion in hot saline.

When partially calcified, a good skiagram will show it as a small elongated shadow, but the completely calcified cyst gives a characteristic appearance (Plate XXII). Evidence of calcification within the brain has been demonstrated. Unfortunately in the early stages the cysts are diaphanous and do not show up. Therefore, a negative radiograph of the skull is of no significance. The size of the cysts depends mostly on their age and situation. Eosinophilia affords no aid to diagnosis. Complement-fixation tests have proved disappointing, and a negative test does not exclude the possibility of infection. The intradermal Casoni test is positive in about 50 per cent. of cases. Trawinski developed a precipitin test, using an antigen made from *Cysticercus cellulosæ*. There may be no changes in the cerebro-spinal fluid. De Sèze and others, however, stated that excess of lymphocytes, a positive colloidal benzoin reaction and eosinophil increase, in the absence of a positive Wasermann reaction, suggest cysticercosis. It must be remembered that the Ghedini-Weinberg complement-fixation, as well as the Casoni intradermal test, are group immunological reactions, whether hydrated extract or cysticercus fluid is used as antigen.

Treatment.—Intravenous injections of antimony tartrate have been tried, often without much effect and, although instances of successful localization and removal of single cerebral cysticercal cysts have been recorded in the literature, usually such interference is unjustifiable. Luminal and bromides are helpful in controlling fits. Observation on tissue changes which follow the death of intracerebral cysticerci suggest that destruction of large numbers of these parasites might make matters worse.

In actual practice, temporary amelioration of symptoms, after removal of one or more cysts, has often been followed by death.

Prophylaxis..—This cannot be undertaken until the source of infection has been ascertained. It is commonly believed that human cysticercosis is an accidental complication, auto-infection being caused by the ingestion of eggs or possibly by regurgitation of segments of *T. solium* into the stomach.

Section X.—DISEASES DUE TO POISONS, INCLUDING SNAKE-BITE, AND INFECTION WITH DIPTEROUS FLIES AND LEECHES

CHAPTER XLV

VEGETABLE POISONS

POISONS USED FOR CRIMINAL PURPOSES

The inorganic poison most generally used by tropical races is arsenic in some form, cleverly intermingled, as a rule, with flour, inserted into the grains of maize or millet, or introduced into sweets, as in Egypt; in Malay, powdered croton seeds or datura are used. Natives usually possess a much wider and more intimate knowledge of organic poisons than do civilized peoples.

In Brazil, common native poisons are derived from *Paullinia pinnata*, which contains an alkaloid, *timboin*, and from the fruit of *Thevetia ahonai*, the active principle of which is *thevetosin*; both of these cause vomiting and respiratory failure.

In the Dutch East Indies a poison extracted from the roots of *Milletia sericea* produces debility, headache, diarrhœa, collapse and death.

In the Pacific islands the native poison is derived from the fruit of *Barringtonia speciosa*.

In India a large number of vegetable poisons is in use. In the Madras and Bombay Presidencies an extract is obtained from the roots of *Nerium odorum*, the white oleander, which contains two glucosides exerting a specific action on the heart. Similar substances, *urechitin* and *urechitoxin*, from *Urechites suberecta*, exert a cumulative action, and therefore sudden death may be produced without arousing suspicion of poisoning.

The juice of an *Asclepias* (or milkweed) is used in India as an infanticide; the symptoms are vomiting, salivation and cramps. The roots of various species of aconite (*Aconitum ferox*, etc.) are used for the same purpose; death takes place rapidly—in three to six hours, as a rule. Several species of Apocynaceæ, such as *Cerbera odollam* and *Thevetia neriifolia*, the sap and seeds of which contain a glucoside, *thevetin*, are very deadly, death from cardiac failure taking place in twelve to fifteen hours. In Southern India, Burma, and Ceylon a decoction of the fruit of *Gloriosa superba*, one of the Liliaceæ, allied to squills, is employed for criminal and suicidal purposes. The active principle, *superbin*, causes gastro-intestinal irritation and cardiac failure within four hours. The commonest poison in India and Ceylon is datura, one o[illegible] t[illegible] deadly nightshades, of which there are several species. The seeds, [illegible] *T. soli*[illegible]od or drink, produce a state of extreme mental exaltation, fol[illegible]al, and [illegible] the active principles are *atropine*, *hyoscyamine*, and *scopolam*[illegible]

In Africa the leaves of *Hyoscya*[illegible]*ezuz*, containing *hyoscyamine* and *scopolamine* as active principles, are [illegible] by Tuaregs of the Sahara. On the West Coast, a decoction of a cactus, colloquially known as "oro," produces blisters in the mouth, vomiting and gastro-intestinal irritation, collapse and death. In China, opium is the suicidal poison most frequently used, especially by women.

DISEASES DUE TO THE INGESTION OF POISONOUS FOODS

LATHYRISM AND FAVISM

This disease, characterized by various nervous manifestations, such as ataxy, spastic paraplegia, weakness and muscular pains, without psychical disturbances, occurs in Abyssinia, Algeria and India in those districts in which vetches, "Khasari," *Lathyrus sativus* and allied species, form the main article of diet. Howard and his colleagues (1923) demonstrated that the wild vetch (*Vicia sativa*), which contaminates this crop, is harmless, but that the poison is contained in a variety, *var. angustifolia,* which contains alkaloids : *vicine* and *divicine.* A similar disease occurs in animals fed upon the same food. The arms and trunk are seldom involved; incontinence of urine and sexual impotence are early and common symptoms. The disease is very chronic and seldom ends fatally. Shah (1939) claimed that cases improve rapidly on dietetic and vitamin treatment, and Anderson (1939) suggested that elements of the vitamin A complex are involved (*see also* p. 398) and that they are effective in treatment.

Favism, an allergic manifestation, due to a bean (*Vicia fava*), produces a syndrome resembling blackwater fever and is common in Sardinia, Greece and the Mediterranean area (*see* p. 76).

ATRIPLICISM

A combination of cutaneous and nervous symptoms in China is caused by eating leaves of *Atriplex littoralis.* The earliest symptoms consist of itching of the hands, followed by œdema, and often by bullæ; the finger-tips may become gangrenous, cutaneous hæmorrhages may occur, and the face and eyelids become cyanotic and œdematous. In many aspects it resembles Raynaud's disease and erythromelalgia. Yu Ky described a syndrome after eating the leaves of *Atriplex serrata,* or *Chenopodium hybridum,* in which the symptoms and signs are similar, and it is thought that the skin lesions can be ascribed to light-sensitive dermatosis.

ACKEE POISONING (VOMITING SICKNESS OF JAMAICA)

An acute and fatal condition, locally termed "the vomiting sickness," has been known for many years in Jamaica. It is found principally in rural districts in circumscribed epidemics. The causation and nature were neither apprehended nor understood, although several Commissions had attempted to elucidate them. To Sir Harold Scott belongs the merit of clearing up this mystery, and of indicating simple and practical methods of prevention, which have saved the lives of many children. It is estimated that since 1886 over 5,000 lives have been lost in Jamaica from this cause.

Vomiting sickness is confined to the West India Islands, practically to Jamaica, and occurs principally in the cooler months, from November to April.

Symptoms.—A previously healthy child suddenly complains of abdominal discomfort, vomits several times, recovers, and perhaps falls asleep. Three or four hours later, vomiting—now of a cerebral type—returns. Within a few minutes, convulsions and coma supervene; and death follows, on an average, about twelve hours from the initial vomiting, though it may take place in one and a half hours. The case-mortality amounts to 80–90 per cent. In those who recover, convalescence is complete in twenty-four hours.

During the attack the temperature is normal or subnormal, rarely rising to 101° F.; the pulse rate is 90 to 100; the respirations are 26 to 30, sometimes, as death approaches, of Cheyne-Stokes type. The pupils are slightly dilated and, until near the end, react to light. Except during the convulsive seizures, there is no muscular rigidity. Post-mortem examination reveals hyperæmia of viscera with a tendency to minute intestinal hæmorrhages, together with marked fatty changes, especially in the liver and kidneys, and sometimes in the pancreas and heart-muscles.

Ætiology.—Scott showed, on what must be regarded as convincing evidence—clinical, seasonal, epidemiological, and experimental—that vomiting sickness is the result of poisoning by a fruit, much used by negroes in Jamaica, called *ackee*, the fruit of *Blighia sapida* (Fig. 187), a tree very common in the island. A similar species is found on the West Coast of Africa, where it is known as *Isin*. When mature and in good condition, this fruit is wholesome enough; if gathered before it is quite ripe and before it has opened while on the tree, or if gathered from an injured branch, or opened after falling to the ground, it is poisonous. The poisonous element in the immature and unsound fruit appears to be soluble in water, for " pot water " in which the ackees have been cooked is much more toxic than cooked fruit. The poison is precipitated by alcohol. Jordan and Burrows showed that the toxic principle is also contained in the seeds and in the arilli of the ackee which have not yet " opened." Evans and Arnold (1938) isolated saponin, which appears to be the toxic agent.

Treatment.—An emetic, and washing out the stomach with an alcoholic fluid during the primary vomiting, are indicated. Scott is insistent that administration of alcohol must be prompt.

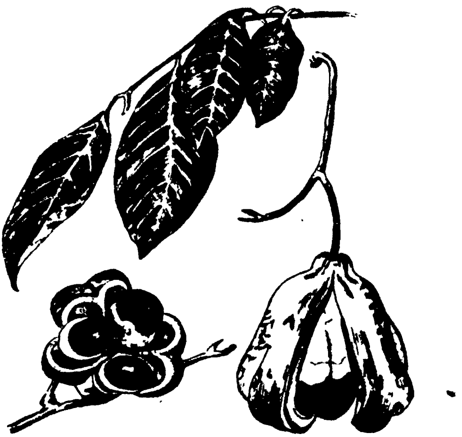


Fig. 187.—Ackee fruit. *Blighia sapida.* ½ nat. size. (*After Byam and Archibald.*)

Prophylaxis. — When the fruit in various stages falls to the ground, only the opened pods, that is the ripe fruit, should be used for food. The immature unopened pods should be destroyed.

MANIOC AND NAMI POISONING

Manihot aipi (sweet cassava) and *Manihot utilissima* (bitter cassava) are ground roots extensively used in the West Indies. From the latter are produced starch, tapioca, and cassava cakes. Poisoning arises from failure to remove the contained glucoside and enzyme. In the presence of water these release free hydrocyanic acid, so that nausea, vomiting, distension of the abdomen and impeded respiration result.

Nami (*Dioscorea hispida*, Dennst, and *D. hirsuta*, Bl.) is a colloquial term for a species of yam, employed for food in parts of the Philippines. It has frequently caused food poisoning, and occasionally it has been put to criminal purposes. An alkaloid—*dioscorine*—has been obtained from the full-grown tubers.

CORAL PLANT (*Jatropha multifida, L.*)

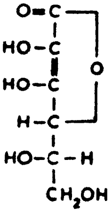
Coral-plant poisoning was reported by Raymond from Tanganyika, the symptoms being colic, cramps and thirst, with subnormal temperature. Two species, *J. curcas* and *J. glandulifera*, are common in the West Indies. *J. glandulifera*, since it grows rapidly, is used in Jamaica for fencing enclosures. The nuts taste like sweet almonds, and the plants are known as " physic nuts " ; a third species, *J. multifida*, is known as the " French physic nut." *J. gossypifolia*, which occurs in the West Indies, is known as the wild cassava, or " belly-ache bush," and its seeds contain an intestinal irritant like croton oil. A fifth species, macrocytic anæmia and to patients with pernicious anæmia caused the same relief, though the anæmia was not markedly improved. B_6 has also been used in pseudohypertrophic muscular dystrophy, in Parkinsonism, in arsenical peripheral neuritis, and in Sydenham's chorea. It has also been found useful in cheilosis (angular stomatitis) which is usually associated with a riboflavin deficiency. Probably both are essential for the nutrition of the lips at the mucocutaneous junction.

VITAMIN C. (ABSORBIC ACID : CEVITAMIC ACID)

Vitamin C forms colourless crystals melting at 192° C. It condenses with aldehydes, acetone and other ketones. The reactions of interest and importance are those dealing with oxidation and reduction. When dry and protected from light, vitamin C is stable for a considerable time, even in the tropics. The indicator of efficacy is 2 : 6–dichlorophenolindophenol. In solution, the stability of vitamin C depends on many factors. Autoclaving at 120° C for twenty minutes in oxygen at *p*H 8 results in the loss of 49 per cent. Solutions of vitamin C can be stabilized by the addition of small amounts of fruit acids, such as tartaric or citric acid.

When vitamin C has been reversibly oxidised to dehydro-ascorbic acid by methylene blue it can be reduced by hydrogen sulphide, cysteine and glutathione.

Ascorbic acid has the following formula :



= *l*-Ascorbic acid (vitamin C).

Dehydroascorbic acid is as potent an antiscorbutic as ascorbic acid.

The I.U. is 0·05 mgm. of pure *l*-ascorbic acid. 1 mgm. of vitamin C is therefore equivalent to 20 I.U., but this standard is no longer used.

Distribution.—Vitamin C is present in all living tissues, especially fresh fruits and plants. The richest sources are rose hips and haws, black and red currants, strawberries, cabbages and citrus fruits. Black currants are sometimes as potent as oranges, in which the greater portion is in the peel. For the majority of people the potato is the most important source. Rose hips in Scotland and N. England contain an average of more than 1000 mgm. per 100 grm. of flesh, whilst those from the south contain less. Properly cooked green vegetables are fairly good sources of C. As soon as vegetables or fruit are gathered, an enzyme—ascorbic acid oxidase—is liberated, which slowly oxidizes vitamin C. They should therefore not be kept too long before cooking ; furthermore, 25–60 per cent. may be lost in the cooking water which is rejected. Stewing and baking tend to destroy vitamin C, so that it is doubtful whether vegetable stews in camps and institutions, cooked slowly for very long periods, ever contain vitamin C. Frying definitely destroys it.

There is no appreciable loss in fruit and vegetables kept in cold storage by the " quick-freeze " process. Drying in itself does not affect C. The antiscorbutic value of fruits and vegetables after commercial canning is no less than that of similar foods cooked by household methods.

The C content of cows' milk is very variable. The value drops as soon as the milk is withdrawn and allowed to cool. Commercial evaporated or condensed milk contains no vitamin C, unless added after processing.

Physiology of vitamin C.—C is synthesized by all higher plants and by many animals, except the primates (including man), the guinea-pig and some ungulates. A function that has been well established is the rôle of vitamin C in regulating the colloidal condition of intercellular substance in the animal organism. It was originally shown by Wolbach and others that in the scorbutic animal reticulum and collagen are not formed, but amorphous ground substance and fibroblasts only are present.

Vitamin C is therefore a prerequisite for the formation of inter-cellular material in man.

Teeth and bones.—Vitamin C plays a part in the nutrition of teeth, joints, bones and blood vessels. The changes in the teeth are as follows : changes in the odontoblasts, widening of Tomes' canals in the dentine, in place of which porous bone-like material (osteodentine) is formed. Pulp tissue becomes atrophied and resorbed. These changes commence in the crown and extend to the root. There is no clinical evidence that dental decay in man is due to vitamin deficiency, but bleeding, soreness of gums and loosening of the teeth do appear to be associated with vitamin C deficiency.

The histological changes in the bones of scorbutic animals are commonest at the costochondral junctions, the distal end of the femur, the proximal end of the tibia and the wrist. Bone formation ceases, and the osseous shell becomes rarefied. Formation of cartilage and bone matrices ceases. Vitamin C is necessary for the proper functioning of the osteoblasts. The periosteum becomes stripped from the bone cortex and lack of intercellular material in the blood vessels leads to subperiosteal hæmorrhages. Vitamin C is also essential for the formation of callus in the union of fractured bones.

Wound repair.—Vitamin C is necessary for wound repair and is usually present in young granulation tissue, and adjoining skin.

Hæmopoiësis.—Anæmia is frequently associated with scurvy, and stimulation of the bone marrow is said to follow injection of C. Clinically, many cases of nutritional anæmia have been described which fail to respond to iron, but react to vitamin C, and it is possible that utilization of iron is defective when the store of vitamin C is depleted.

Infection and immunity.—A considerable amount of indirect evidence has been offered for a relationship between vitamin C and infection. Animal experiments tend to show that C has an effect on the production of antibodies. It also possesses bactericidal and bacteriostatic powers and inactivates certain toxins, such as those of *Clostridium œdematiens*, *Bact. dysenteriæ*, and *Clostridium tetani*. Recently it has been suggested that there is close relationship between C in the body and the degree of complement quantities by the leucocytes in the blood, and also some support for the view that it is important in detoxicating processes in the body. Patients showing sensitivity to arsphenamines are said to have low vitamin C levels.

Function of vitamin C in tissues.—It is suggested that C is a component of a reversible oxidation-reduction system acting as a hydrogen transporter or respiratory catalyst. It has been shown, for instance, that *alkaptonuria*, in which homogentisic acid is excreted, turning the urine black, may be produced by administration of amino-acid tyrosine on a diet low in vitamin C. This vitamin is particularly abundant in the corpus luteum, the pituitary, the adrenals and glandular tissue. It is possible that it plays an important part in metabolism of the adrenals and may serve to stabilize the medullary (adrenalin) and the cortical hormones.

It is true that certain symptoms of scurvy resemble those of adrenal insufficiency. There is also a possible relationship between C and function of the thyroid gland. It may be that it antagonizes thyrotoxin.

Carbohydrate metabolism.—When given by the mouth C has no effect on the blood sugar level, but, when given intravenously, the blood sugar drops in a normal individual. From the high C content of active tissues it is considered that it is essential for synthetic processes in the cell.

Absorption and storage.—Vitamin C is selectively absorbed by tissues of the intestinal tract, chiefly by those of the small intestine, and it has long been known that patients suffering from gastro-intestinal diseases excrete subnormal amounts of C in the urine ; there is some evidence that it is inadequately absorbed in patients with achlorhydria.

It is evident that C must be stored in the body, because human scurvy takes several months to develop in diets deficient in this vitamin. It appears to be stored in organs and tissues with high metabolic activity and is present to a great extent in tissues of the young. (The adrenals are the organs richest in C and a considerable amount is present in the lens of the eye). In normal subjects the vitamin C content of the blood plasma ranges from 0·6 to 2·5 mgm. per 100 c.c.

Excretion.—Vitamin C is excreted in the fæces and sweat, but the bulk passes out in the urine, and the rate of excretion depends upon the intake. When administration is continued long enough, the tissues become saturated and a rapid rise in urinary excretion occurs. A daily urinary excretion of 18 mgm. represents the borderline between deficient and adequate intake. Various drugs affect the excretion, especially ammonium chloride. Insulin causes a lowered urinary excretion.

Determination of capillary fragility.—The capillary fragility tests serve as a measure of the physiological indispensable minimum requirement. From simultaneous determinations of capillary fragility tests and blood ascorbic levels it has been found that capillary fragility becomes pathological at blood values between 0·1 and 0·14 mgm. of C per 100 c.c. Blood vitamin C values above 1·4 mgm. per cent. constitute the threshold value and correspond to a state of vitamin C saturation.

Human requirements.—The indispensable minimum is between 25 and 30 mgm. a day—0·4 to 0·5 mgm. per kilo. of bodyweight. The optimum is 50–75 mgm. daily, but more is needed in pregnancy, old age and acute infections.

The fœtus withdraws vitamin C from the mother through the placenta, and the concentration in the blood plasma of the umbilical cord is one and a half to four times as much as that present in the maternal blood at the time of delivery. There is a rapid decrease in vitamin C content during the first few weeks of life, suggesting that vitamin C should be regularly supplied ; the content of the breast-fed infant depends on the mother's intake. The requirements of children are greater proportionately than those of adults. The requirement of boys from 13–15 is 90 mgm. daily ; that of adults from 30–100 mgm. In women this is naturally increased during pregnancy and lactation. In all infectious conditions the requirement is increased.

Laboratory methods employed for detecting vitamin C deficiency —*Capillary fragility test.* (Rumpel-Leeds test.)—A circular area 60 mm. in diameter is marked off in the antecubital fossa and a blood pressure cuff placed at least 2·5 cm. above this, pumped up to 90 mm. mercury and maintained for fifteen minutes. After the pressure is reduced the number of petechiæ is counted. The test should be carried out at room temperature and the patient should not have had a hot bath on the day of the test or take any exercise within three hours.

The intradermal test.—This depends upon the power of vitamin C in the skin to decolourize the blue dye, 2 : 6—dichlorophenolindophenol, of which 0·1 c.c. of a 1 : 400 dilution is injected into the anterior surface of the forearm. When the individual is saturated the skin is decolourized in less than five minutes ; unsaturated individuals require ten minutes or longer.

Urinary excretion.—Some authorities consider that the twenty-four hour excretion of vitamin is reliable for detection of C deficiency. The method of estimation is to determine the amount of urine which has to be added to discharge the colour of a measured quantity of 2 : 6 dichlorophenolindophenol, but it must be remembered that other substances in the urine, such as cysteine and thiosulphates, may also act the same way.

A somewhat similar test has been developed for estimation of vitamin C in the serum.

Clinical uses of vitamin C.—The only disease which specifically responds to vitamin C is scurvy, yet its use has been advocated in the treatment of a number of conditions, such as the zymotic diseases, especially diphtheria. It has also been used in pneumonia, tuberculosis, rheumatism, whooping cough, typhoid, infections of the ear and throat, influenza, malaria, dental and oral conditions, hæmorrhagic diseases, some forms of pernicious anæmia, skin diseases and to an increasing extent in surgery, obstetrics and ophthalmology.

VITAMIN D. (ANTIRACHITIC OR CALCIFYING VITAMIN)

Several substances are antirachitic. The most important are :—

Vitamin D_2 (calciferol). This does not occur naturally, but is manufactured artificially by " activating " ergosterol.

Vitamin D_3, sterol–7–dehydrocholesterol, is the most important naturally-occurring vitamin, being formed in the skin by the action of the sun on the animal. It has the same action as D_2. The chemistry of the sterols is extremely complex. Vitamin D_2 is made by exposing ergosterol to the action of ultra-violet light. The absorption spectrum gives bands of maximum intensity at $260–298\mu$. Ergosterol is best irradiated in solution, It is a white crystalline substance, melting at 115–117° C. It is stable at room temperature and loses its antirachitic properties at 180° C, but is completely stable dissolved in oil kept at 0° C. Biological assay is the only means available of chemical estimation.

Distribution.—Ergosterol is only found in plants, especially fungi, like ergot from which it derives its name. D_3 is found in egg-yolk, butter and fish oils. Animals gain vitamin D by eating tissues containing it or by direct action of the sun's rays on the provitamin in their own skins. Food *per se* as a source of D is not so important. The formation of vitamin appears to occur *on* the skin. Thus, in birds it takes place in the oil of the preen glands, so that when this is artificially removed they develop rickets.

Nothing definite is known on how fish acquire D though it is probable that they are able to synthesize it.

Assimilation.—In birds and animals the vitamin formed on feather or fur is swallowed during preening and licking, but in man it must be absorbed from the skin because irradiation will cure rickets. Bile is essential for its absorption from the intestine, but liquid paraffin or oil hinder, because it is thereby dissolved and excreted in the fæces. It is also possible that it hinders the absorption of calcium and phosphorus.

Storage.—Various tissues store D for different periods: the brain for 1–2 weeks; the kidneys and liver and blood for 8–12 weeks. Depletion is caused by its excretion into the gut and destruction in the body.

Rachitic diets.—The composition of the diet has a great effect in rickets. The usual diet is one which contains an excess of calcium and acts by forming insoluble phosphates. The bad effect of cereals, especially oatmeal, is well known. This is due to the *phytic acid* of the cereals combining with the calcium of the diet, causing calcium deficiency. The amount of fat in the diet is important as it counteracts the effect of cereals.

Physiology of D.—*Calcification.*—This vitamin regulates the metabolism of calcium and phosphorus, but its mode of action is still obscure. During growth long bones increase in length by calcification of the cartilage between diaphysis and epiphysis. The cartilage is continuously growing on the epiphyseal side, and degenerating on the diaphyseal, which is then invaded by capillaries and osteoblasts. Bone salts are laid down in the degenerating cartilage. In rickets the band of cartilage widens because it keeps on growing, but ceases to degenerate, and no calcification takes place. This results in weakening of the bones, with subsequent bending and fracture. The X-ray picture in severe rickets shows these changes; the end of the diaphysis is smooth, with a clear space between it and the epiphysis. In rickets the end of the diaphysis is uneven and ragged because of the degeneration of the cartilage. The shaft of the bone also shows rarefaction.

When healing commences under the influence of D the first effect is resumption of degeneration of the cartilage cells nearest to the diaphysis, which is rapidly followed by capillary penetration and laying down of bone salts. The rôle of D in calcification of teeth is important.

The amounts of calcium and inorganic phosphorus in the serum are altered; the phosphatase of the blood is raised in rickets and to a lesser degree in osteomalacia. The skeletal muscles and the smooth muscle of the gut lose their tone and the ligaments become lax. Stimulation of growth, as apart from the prevention of rickets, is an important function of vitamin D.

The relation of D to the endocrine glands is important and has a stimulating effect on the parathyroids particularly, and to a lesser extent on the thyroids and pituitary.

The relation to infection is obscure, especially the effect of cod-liver oil on tuberculosis, in which it may possibly exert a specific effect.

Excessive dosage mobilizes the phosphorus and calcium from the body tissues, thus broadly exerting the opposite effect of normal doses. The tubules of the kidney and the media of the larger blood vessels are affected. In the aorta atheromatous changes become evident. The serum phosphorus and calcium are usually grossly raised.

International Unit.—The *I.U.* is the amount of D equal in antirachitic potency to 1 mgm. of the international standard solution, which is equal to 0·025 microgramme (γ) of crystalline D_2 (calciferol).

Estimation.—The "*line test*" is based on the cure of rickets. This is done by feeding identical groups of rats on a rachitic diet until rickets develops. To the diet of one group a standard preparation of D is added. The bone developed during the curative period is stained with silver nitrate and appears as a black line.

The bone ash method depends on the prevention of rickets. Groups of rats are fed for four to six weeks with varying levels of the standard preparation being tested. They are then killed and the femoral bones ashed, when comparison of the ash from various groups of animals shows how much calcification has occurred.

Sources of vitamin D for man.—Sunlight acting directly on the body is the most natural source, but when in excess may cause not only severe sunburn, but fever, malaise and shock. The activated fat is apt to be washed off by bathing.

Artificial sunlight, given by either the carbon arc or mercury vapour quartz lamp, is an excellent substitute for sunlight and has the same effect in prevention and cure of rickets.

Food.—The dietetic sources of D in normal foods are dairy produce, fish and dripping. Green vegetables contain none. The value of all dairy produce depends on the diet and exposure to sunlight of hens and cows. Hence eggs contain nearly three times as much D in summer as in winter. Milk is an extremely valuable source, and may be artificially reinforced, either by irradiating the cow or its milk, or by adding D to the cow's diet.

In concentrated preparations of natural and artificial D it has been shown that 200–500 I.U. given daily as cod-liver oil is sufficient to prevent rickets, while 400–800 I.U. of calciferol is necessary to produce the same effect. There is a risk of hypervitaminosis when excessive doses of calciferol are taken.

Human requirements.—If the diet is not grossly abnormal, especially for calcium and phosphorus, the amounts required at various ages may be stated as follows:

Premature infants	600–800 I.U.
Pregnancy and lactation	600–900 ,,
Infants	300–600 ,,
Children at puberty and adolescence ..	300–600 ,,
Adults, male and female	300–600 ,,

In old age the value of sunlight is often lost, so that the diet should be supplemented with cod-liver oil to prevent osteoporosis.

Diseases due to lack of vitamin D.—The commonest is rickets which, contrary to general belief, is still widespread. The rachitic infant develops slowly, is liable to infection and does not attain full stature. Rickets can, however, occur at any age. Infants have been born with rickets, and "late rickets" or "juvenile osteomalacia" may occasionally be found in older children, especially during periods of rapid growth. The clinical picture of rickets is well-known and may be accompanied by pelvic distortion and "greenstick" fractures.

Spasmophilia is due to nervous symptoms of which the underlying factor is a lowered blood calcium. This expresses itself in general irritability, laryngismus stridulus and convulsions.

Other forms of rickets are cœliac rickets, scurvy-rickets, renal rickets and osteomalacia. Osteomalacia of pregnancy, hunger osteomalacia and senile osteoporosis are fundamentally the same, and are due to lack of vitamin D. Tetany is common.

Effect of vitamin D on the teeth.—In rachitic children teeth tend to erupt late and decay early, which appears to be direct effect of lack of this vitamin, but in osteomalacia the teeth do not decay unduly. It therefore appears that vitamin D is not necessary for good teeth in either children or adults, but it is probably valuable in helping to protect them.

Symptoms of vitamin D poisoning.—Loss of appetite follows quickly on the sense of well-being, and then come loss of weight, weariness, weakness and profound mental depression. Death may take place.

Note.—The remaining vitamins —E, K, P— and other less well-defined substances recently described, have been omitted as having little bearing on the subject matter of this book.

CHAPTER XXIV

BERIBERI

Synonyms.—Kakke; Barbiers; Polyneuritis Endemica.

Definition.—Beriberi is a form of multiple peripheral neuritis occurring endemically, or as an epidemic, in most tropical and sub-tropical climates, and also, under certain conditions, in more temperate latitudes. The mortality may be considerable, usually from cardiac failure.

History.—Beriberi was originally described by the early Chinese physicians, and is said to be referred to in the Neiching, a medical work attributed to Hwangti (B.C. 2697). The special nature of beriberi was recognized by the Dutch in their early years in the East. Later, it was studied by British physicians in India, particularly by Malcomsen, Carter, Waring, and Morehead. It was not until an epidemic in Brazil that beriberi began to receive attention from a later generation of medical men; and only when Anderson, Simmons, Scheube and Baelz took up the subject in Japan was it studied by modern methods, accurately defined, and its true pathology apprehended. Scheube and Baelz were the first to show distinctly that beriberi is a peripheral neuritis simulating that of diphtheria and of alcohol—a view subsequently confirmed and adopted by Pekelharing and Winkler, and by most subsequent observers. Mainly owing to the investigations of Eijkman, Grijns (1901), Braddon, Cooper, Fraser, Stanton, Funk, Vedder, Hopkins, Hausette, Chick and Margaret Hume, its principal—it may not be the only—ætiological factor has been shown to be a dietary of which the staple ingredient is overmilled rice or other cereal which has been deprived of vitamin B_1.

Geographical distribution.—The area of the endemic distribution of beriberi is co-extensive, probably, with the tropical and subtropical belts. It was formerly the scourge of many of the mines and plantations of the Malay and Eastern Archipelago. It was apt to break out among the coolie gangs engaged on extensive engineering works in the tropics, such as the Panama Canal or the Congo Railway. It haunted the Dutch army in Sumatra, used to be common enough in the British armies in India and was the scourge of the Japanese navy. It is still found in many parts of Japan, particularly in her large, low-lying, damp, overcrowded cities. It occurs in China, the Philippines, the Eastern Peninsula, India, and Africa. We have had accounts of a small epidemic among a group of Western Australian natives, and also among Chinese on the eastern seaboard of Australia, a continent where beriberi was formerly supposed not to exist. Many years ago beriberi broke out in a lunatic asylum in Dublin; and apparently the same disease has been seen in similar institutions in the United States and in France, and also among the Newfoundland fishermen and those on the North American coast. Tomasson reported (1938) an epidemic in the Westman Islands, Iceland. The diet consisted of fresh fish which, even in large quantities, is deficient in vitamin B_1. Elshout and Lentjes described a similar outbreak amongst prisoners on an island off Holland.

Epidemiology and endemiology.—*Sex, age, occupation.*—Beriberi attacks both sexes. It is not uncommon in the breast-fed infants of beriberic mothers. This form, called *infantile beriberi*, may declare itself in varying ways.

Ship beriberi.—Beriberi is prevalent among the native crews, more rarely, From 1894 up to 1920, or thereabouts, the disease was common in European crews of Swedish and Norwegian ships, which are in far better sanitary condition than British ships, and yet beriberi is comparatively rare in the latter. The modern explanation is that, since the year named, the crews of the Norwegian mercantile marine have been provided, under the terms of a statute, with bread baked from white flour, or a mixture of wheat and rye, so that their diet is inadequate in vitamins. Ship beriberi holds a place intermediate between true beriberi and scurvy, and is closely related to the disease found among the Rand miners of South Africa. A similar disease has recently been noted amongst the whale fishers of South Georgia. In Newfoundland beriberi of both forms is found at times when the diet is reduced to a regime of bread and molasses (Aykroyd). A number of cases have been reported from H.M. ships in the Persian Gulf.

Asylum beriberi.—The Dublin lunatic asylum, built for 1,000 inmates, had 1,500 inmates crowded into it when beriberi broke out, due to dietetic causes.

Ætiology.—The earliest investigators of beriberi believed that it was a degenerative multiple neuritis indistinguishable from that produced by alcohol or diphtheria, and that it was due to an infection or intoxication, and much effort was directed to the discovery of the poison. All these theories are now a matter of history, for they have been replaced by the vitamin-deficiency theory.

History.—Lunin (1881) found that mice could not survive on artificially composed milk. Socin (1891) and Pekelharing (1905) postulated some substance necessary for nutrition. Eijkman (1890) and later Grijns proved the existence of a food deficiency in beriberi. Braddon (1907), later Fraser and Stanton established the correctness of these observations in man in Malaya, and Hopkins in England devised experiments directed to the recognition of food constituents necessary for growth. Funk (1911), in attempting to isolate the principle from rice-polishings, coined the word *vitamin*. The water-soluble vitamin was found essential for growth by McCollum and Davis (1915) The isolation of the principle was made possible by the work of Sidell (1916), Kimersley and Peters (1924), and finally the isolation of vitamin B_1 was effected by Jansen and Donath (1926). The chemical constitution was established by Windaus *et al* (1932), Williams *et al* (1935), the synthesis by Williams (1936), Bergel and Todd (1936), Andersag and Westphal (1936).

Thanks to this pioneer work, we know that the beriberi of the Eastern Peninsula, of the Eastern Archipelago, of the Philippines, of China and of Japan, is a sequel of a diet in which overmilled rice is the principal element, that is, rice from which the entire pericarp and germ have been removed; and that in this pericarp and germ there is a substance essential to the proper nutrition of the nervous system of man and of many other warm-blooded vertebrates.

If a fowl or pigeon be fed exclusively on "*paddi*," that is, rice from which the husk has not been removed, it will thrive and very likely gain weight; but if it be fed exclusively on a diet of white rice and grain, that is, rice from which the pericarp has been completely removed, after a short time it will show signs of peripheral neuritis, lose weight and, if the exclusive diet be persisted in, die with all the signs of a multiple peripheral neuritis. This *polyneuritis gallinarum* (or *p. columbarum*)—as it is called—is evidently the result of the deprivation of some

Milled r
polished

Fig. 56.—Showing the various stages in milling the rice grain. 1, Rice grain in the natural condition enclosed in the husk or enclosing glumes; 2, After removal of the husk, but retaining the pericarp or "silver-skin" and the embryo; 3, After milling and polishing; both "silver-skin" and embryo are removed and the grains are "polished" by rubbing with talc between sheepskins. (*After Chick and Hume, "Trans. Soc. Trop. Med. and Hyg."*)

Fig. 57.—Diagram of longitudinal section through a grain of wheat showing (a) aleurone layer of cells forming the outermost layer of the endosperm, removed with the pericarp during milling; (b) pericarp forming the branny envelope; (c) parenchymatous cells of the endosperm; (g) embryo or germ. (*By permission of H. M. Stationery Office, from Dr. J. M. Hamill's "Report on the Value of Bread made from Different Varieties of Wheat."*)

colour from red to white according to the variety of the rice. The pericarp contains the salts. The grain itself is covered by a husk, which is discarded as chaff.

Conditions under which rice is grown.—Rice grows normally in puddled fields in which a layer of water is allowed to remain until the grain is almost ready for reaping, and this puddled rice has a nutritional value of approximately one-third less than the same rice grown under dry rain-fed conditions; it contains also a lower content of vitamin B_1; the Chinese eat mostly polished rice, normally

from fresh vegetables, shortage of which has from time to time led to a great increase of beriberi in Malaya. (*See also* Chap. II, p. 29.)

Fraser and Stanton showed—and their observations have been abundantly confirmed—that the antineuritic element is located in the pericarp of the rice grain, in the aleurone layer, and in the embryo of the grain, that it is soluble in water and alcohol, is stable in acid but unstable in alkaline solutions, is thermolabile—being destroyed by a temperature of 130° C.—and that it is dialysable; that it is not a phytin or a fat, and that, although itself not containing phosphorus, the amount in any given rice is a reliable indication of the safety, or otherwise, of that rice as a staple article of food. Rice containing less than 0·4 per cent. of P_2O_5 they considered unsafe, and believed that its persistent use may lead to beriberi.

The polyneuritis of the fowl is identical clinically and ætiologically with the polyneuritis, called beriberi, occurring in man. For, as has been both accidentally and intentionally done, if the same experiment with rice-feeding be tried on man the result is identical—beriberi is induced. Thus, following the lines of the earlier experiments of Fletcher, Fraser, and Stanton, Strong and Crowell conducted a series of experiments on twenty-four life-sentenced prisoners, and were able to prove (*a*) the non-communicability of the disease, and (*b*) its production in man solely by means of diet. A similar condition has been produced in rats.

Acting on these findings, the governments of Singapore and the Federated Malay States forbade the use of white or polished rice in their jails, lunatic asylums, schools and hospitals, with the result that beriberi, which until then had been the cause of an enormous mortality and morbidity, has been practically banished. Corresponding results have accrued from the same practice in Dutch East Indies, the Philippines, and elsewhere. In India decorticated rice is practically the staple diet of many millions, though beriberi is endemic only in a few circumscribed areas in Bengal and Assam, the north-east coast of Madras, the coast of Burma, and certain river valleys. The basal factor in India must be a fundamentally poor diet, whether of rice or other food grains. The period of development of beriberi in man was determined by Fraser and Stanton as between eighty and ninety days. The part that vitamin B_1* plays in beriberi is now becoming clearer. Walshe (1941) claimed that, both clinically and pathologically, beriberi is a typical polyneuritis, differing in no essential from other varieties. The nervous signs and symptoms are those of a multiple symmetrical nervous lesion, the cardiac manifestations those of polyneuritis.

It is, however, clear that deprivation of B_1 alone is not sufficient to cause beriberi in fowls or man, for patients dying of anorexia nervosa do not develop polyneuritis. The significance of B_1 is in relation to carbohydrate metabolism, rather than to its direct effect on the nervous system. Human and avian nervous systems can be deprived of B_1 with impunity when no carbohydrates are given. B_1 acts as a catalyst in carbohydrate metabolism of the nerve cell and heart muscle. In the absence of B_1, cellular carbohydrate metabolism breaks down at the stage of pyruvic-acid formation. This substance accumulates in the cells, where its presence can be detected. It is, however, an error to suppose that pyruvic acid is toxic. Peters and his colleagues believe that B_1 functions as a co-enzyme in the metabolism of carbohydrates and plays a part in the oxidation breakdown of pyruvic acid. Therefore accumulation of this acid or of pyruvates in the blood and central nervous system, and its excess in the urine, is related to the deficiency of B_1. It is therefore essential for normal growth and the maintenance of body weight.

---

* An account of the chemistry, physiology and pharmacology is given on p. 400.

Incidence.—The incidence of beriberi is greatest in those regions where polished rice and refined cereals form the bulk of the diet. It constitutes one of the most potent causes of mortality in Japanese infants. From 1920–1929 there was an average of 17,000 deaths from this cause in Japan. Berberi appeared in the beleaguered troops at the siege of Kut in 1916. Balfour stated that every pregnant woman in S. India suffers from it. In S. China beriberi is common in the later months of pregnancy and in the puerperium.

In people living on an inadequate diet the raised basal metabolic rate resulting from fever increases the liability to beriberi—as after smallpox, cholera or meningitis. In China, for instance, 10 per cent. of patients show some reflex abnormality suggesting latent beriberi. Thus, any lowering of the general resistance leads to the development of polyneuritis. Breast-fed babies born of mothers suffering from the disease are themselves liable to it.

Pathology.—The post-mortem appearances of beriberi resemble the accepted descriptions of peripheral neuritis. There is a degeneration of the peripheral nerves—more especially of their distal ends—and there is secondary atrophic degeneration of muscle, including that of the heart. Degenerative nerve-changes may be detected in the nerve-centres and throughout the implicated neurones, as in other forms of peripheral neuritis. There is invariably an involvement of the vagus, with degenerative changes in its root in the floor of the fourth ventricle. Microscopically, the nerve-trucks show changes, from a slight medullary degeneration to complete destruction of the nerve (Wallerian degeneration). Regenerative processes occur side by side with the degenerative (Fig. 58). As a rule, some fibres in the vagus and sympathetic escape; thus, the cardiac branches in the heart-muscle and the bronchial and œsophageal twigs are usually unaffected. According to Vedder, the membranes of the spinal cord are often congested and œdematous; scattered fibres in all tracts show the same kind of changes as the peripheral nerves. Degenerative changes are also found in the anterior and posterior horn cells, as well as in the sympathetic ganglia. If there is anything peculiar about the post-mortem appearances in beriberi, it arises from the somewhat special implication of the central and peripheral organs of the circulation—namely, dilatation of the heart, especially of the right side, and great accumulation of blood in the right heart and in the veins. In addition, there is a marked liability in many cases to serous effusion into the pericardium, pleural cavities, peritoneum, and cellular tissue. This very marked liability to serous effusion and the tendency to cardiac dilatation may be said to be more or less distinctive of beriberi as compared with other forms of multiple neuritis. Œdema of the cardiac muscle naturally interferes with the normal fluid exchange within the fibres and therefore with its contractibility. According to Mebius, when vitamin B_1 is deficient, full muscular contractibility is impossible owing to water absorption (hydropic degeneration of Wenckebach). The average weight of the Japanese heart in beriberi is 368 grm. (normal 300 grm.). The enlargement is particularly noticeable on the right side, especially the right auricle, and the walls are paper-thin. Without doubt, water-retention in beriberi is of the greatest importance in elucidating the mechanism of symptom production. Œdema of the lungs also is not uncommon, and has, probably, a pathology

88.—Longitudinal section of external popliteal nerve in beriberi.

One medullated fibre in centre is practically intact; the others show typical fragmentation of myelin sheath with swelling of remains of nerve-fibre.

(*From a preparation by Dr. A. C. Stevenson.*)

Symptoms. *Primary Beriberi* (*Naturally-occurring disease*).—Beriberi assumes varying clinical forms according to the extent and position of the nervous lesions. It is insidious in onset, but it may occasionally be ushered in by acute symptoms ending fatally within a few hours without development of any symptoms referable to the nervous system. As a general rule, it is classified into two main forms, according as the peripheral nerves or the cardiovascular system are most affected. The former is known as paraplegic or "dry" berberi, the latter as œdematous or "wet" beriberi. It must be understood that in all its forms beriberi is the same disease, and that a clinical classification has but a conventional value. Sudden death from heart failure may ensue, especially in œdematous cases.

Fig. 59.—Ataxic or paraplegic beriberi, showing characteristic attitude.

roughly, particularly if they are squeezed against the underlying bones, the patient will call out in pain and try to drag the limb away. Toe and foot-drop can frequently be demonstrated. Weakness spreads upwards, first involving the extensor muscles of the leg, and then the extensors and flexors of the thigh. The skin of the limbs becomes shiny. The thenar, hypothenar, plantar and arm muscles, like the calf muscles, may be wasted and flabby and exhibit fibrillary twitchings. Very probably there is a loss of fat, the panniculus adiposus being everywhere meagre. If tested electrically, the

Fig. 60.—Paraplegic beriberi, showing wasting of extensor muscles and wrist-drop.

or perhaps he cannot; he may bungle and fumble like the advanced ataxic. The fibres of the affected muscles, when struck with a patellar hammer, often contract locally in a particularly painful manner known as myœdema. There may be wrist drop (Fig. 60).

There is more than ataxia, however, for the hand-grasp is so enfeebled that the patient may have a difficulty in holding his rice-bowl as well as in feeding himself. There is no tremor of the hands; and never, or very rarely, is there any paresis of the ocular muscles, or of the muscles of the face, of mastication, of the tongue, or of the pharynx. The sphincters and bladder operate satisfactorily, and the functions of the alimentary canal are carried on fairly well, although there is often some dyspeptic distension and oppression after food. If the patient can walk at all, his gait will nation of the scanty, dark-coloured urine shows that it is of high specific gravity and contains no albumin, or only a mere trace. Careful observation will discover that the œdema is somewhat firmer than that of nephritis and, in not a few instances, that it does not involve the scrotum. Occasionally it is peculiarly localized and fugitive. A bruit and other evidences of dilatation of the heart are discovered.

Occasionally irregularity may be associated with slowing of the heart-beat, and heart-block may occur in such cases. The liver is frequently swollen and tender. The lungs may (or may not) present signs of single or double hydrothorax, but they themselves are healthy. The patient can hardly walk—partly from breathlessness, partly on account of mechanical interference by the dropsy with the movements of the legs, partly, perhaps, from some degree of paresis. He may have ankle-drop ; if firm pressure be brought to bear on the calf-muscles through the œdema, signs of hyperæsthesia of the muscles may or may not be elicited. Knee-jerks are generally absent, and there is numbness of the shins and finger-tips. The tongue is clean, the appetite fair, and there is no fever. But there may be præcordial distress and even pain, and, as this is aggravated by a full meal, the patient eats sparingly. The amount of urine is generally very much reduced—even to a few ounces.

In this patient, therefore, there are the same signs of peripheral neuritis and of dilatation of the heart as in the other cases. In addition, there is a somewhat firm œdema, which is not altogether cardiac, but, as its character and the circumstances in which it is found suggest, is probably connected with the play of transudation and absorption in the connective tissues.

When the heart is examined, if the case be at all recent or moderately severe, the impulse is diffuse ; there is epigastric pulsation ; the carotids throb too violently ; and there is that peculiar wobbling, pulsating movement in the jugulars that denotes tricuspid insufficiency. " Pistol shot " sounds are heard on auscultation over the larger arteries. On percussion the præcordial area is frequently enlarged, perhaps very greatly enlarged, especially to the right ; and on auscultation loud bruits, usually systolic in rhythm, may be heard. Marked reduplication of the sounds, particularly of the second, is noted. The auscultator may be impressed, in a large proportion of cases, by the peculiar spacing of the intervals between the sounds. It may be hardly possible to tell by the ear alone which is the first pause and which is the second. They seem alike in point of duration (tic-tac rhythm) ; so that the sounds resemble the beats of a well-hung pendulum clock, evenly spaced, and not, as they are in health, separated by a long and a short interval. It will also be observed that the heart is very irritable, easily quickened by exertion. In addition to peripheral neuritis, there is serious disease in the circulatory system, particularly in its innervation ; there is dilatation of the right side of the heart, and a state of relaxed arterial tension. Paralysis of the left recurrent laryngeal nerve by a grossly distended right auricle has been recorded. There is a wide range in the pulse-pressure, and Aalsmeer and Richter have shown that there is almost invariably a low diastolic blood-pressure which can be influenced by the injection of adrenalin (the adrenalin effect). Pitressin raises the diastolic pressure from almost zero to 75 mm. and the venous pressure falls ; this beneficial effect may last 1¾ hours.

Usually in well marked cases, the electrocardiagram shows distinct changes of low voltage and an indefinite inverted or flattened T wave in I, II and III leads, shrinking of the P—R interval and prolongation of the Q—T interval.
The cardiac enlargement in human beriberi was ascribed by Aalsmeer and

Wenckebach to œdema of the heart-muscle, which results in an interference with its contractile power without disturbance of its excitability.

Wenckebach investigated a number of cases of cardiac beriberi in the Dutch East Indies and Singapore, taking special precautions to inject hardening fluid, and he was thereby able to confirm the presence of certain gross anatomical changes which are demonstrable during life by radiography. The whole of the right side of the heart is enlarged, while the left remains comparatively small; the conus arteriosus takes part in the change. The large systemic veins are commonly dilated, and as much as three litres of blood may escape from the right auricle. The extrapericardial pulmonary vessels are not abnormally congested. Microscopic examination of the heart muscle after death reveal intracellular œdema, sarcolysis, and hydropic degeneration, probably primarily due to excess of lactic acid, brought about by defective oxygenation. The primary lesion is, therefore, a loss of contractibility of the heart muscle, related to water retention, with consequent loss of peripheral vascular tone. The clinical picture and its response to adrenalin and pitressin, together with the lowering of diastolic pressure, accord with these findings.

Aalsmeer employed the results of these observations as a practical test to indicate the stage of the disease and response to treatment. The diastolic pressure is known as the " minimum tone pressure," because it is the pressure registered by the sphygmomanometer at the moment when the auscultatory bruit disappears with decompression of the brachial artery. The essence of the test is that, when the diastolic pressure is registered, the administration of adrenalin in hypodermic doses of 1 mgm. will be found, if observations are taken at five-minute intervals, to bring the pressure down to zero in an uncured case of beriberi. That is to say, the auscultatory murmur will persist during complete relaxation of the pressure of the artery as long as the patient is under the influence of adrenalin.

Cardiac attacks.—Most cases die from paresis and over-distension of the right heart, complicated and aggravated by œdema of the lungs, diaphragmatic paralysis, hydrothorax or hydropericardium. Sudden cardiac failure (termed by the Japanese " Shôshin ") is often contributed to by the co-existence of pleural effusion, hydropericardium, paresis of the diaphragm, over-distension of the stomach by food or gas, and, above all, by œdema of the lungs. It can readily be understood how any additional obstruction of this description would still further tax the dilated, enfeebled heart and determine the fatal issue.

Great variety in degree and combination of symptoms.—Some cases are so trifling that the patients are up and moving about with more or less freedom; others lie like logs in their beds, unable to move a limb or perhaps even a finger. Some are atrophied to skeletons, others are swollen out with dropsy, and some show just sufficient dropsy to conceal the atrophy of muscles. Though the cranial nerves above the seventh are very rarely involved, in some the laryngeal muscles are paralysed, the patient being unable to speak above a whisper or to produce an explosive cough. In one or two cases the abdominal and the perineal muscles may be so profoundly paralysed that, when cough is attempted, at most a husky expiration is produced, while the belly is bulged forward and the perineum shot downward by the sudden contraction of the muscles of expiration. The deep reflexes do not reappear for months, perhaps, after the patient is well in all other respects. In some epidemic outbreaks, as, for instance, in Iraq in 1916, an irregular *pyrexia*, seldom exceeding 100° F., was noted.

Uncertain course.—Beriberi slowly or rapidly declares itself after an incubation period of weeks or months.; it may be preceded by a period of intermitting languor, aching legs, palpitations, breathlessness, slowly advancing œdema of legs or face; or the patient may wake up some morning and find that during the night he has become dropsical or paretic. Thus, the disease may develop slowly or rapidly. Equally uncertain are its progress and danger; within a day or a week, or at any time during its course, it may assume fulminating malignant characters. It may completely subside in a few days, or it may drag on for months. It may get well apparently and then relapse. It may, and generally does, clear up completely; or it may leave a dilated heart, or atrophied limb muscles with corresponding deformity. The variety in the severity, progress and duration of beriberi is infinite; but in all cases the essential symptoms are the same—greater or less œdema, especially over the shins; muscular feebleness and hyperæsthesia, especially of the legs: numbness, especially of the front of the shins, of the finger-tips, occasionally of the lips; liability to palpitation from cardiac dilatation, and to sudden death from the same cause.

Secondary beriberi. *Beriberi manifestations produced by other diseases. Alcoholic beriberi.*—It has long been recognized that alcoholic neuritis resembles in many respects the paraplegic form of beriberi. It resembles it so closely that in recent years the idea has gained ground that this resemblance is more than fortuitous, and that in both conditions there is an antecedent deficiency of vitamin B_1. The theoretical considerations advanced by Shattuck have led to the recognition of a variety of intestinal conditions in which polyneuritis may occur, such as gastric carcinoma, chronic intestinal obstruction, and ulcerative colitis, and, in the opinion of some observers, all these should be included under the heading of secondary beriberi. Cases have been reported of alcoholic addicts with congestive heart failure and polyneuritis who have recovered completely after treatment by rest, a high-calorie diet, and vitamin B_1.

Multiple factors are probably concerned in the production of alcoholic beriberi, including defects in diet and assimilation acting in conjunction with increased tissue requirements for vitamin B_1 due to an increased rate or type of metabolism. Many cases of alcoholic neuritis have now been cured by the continued injection of aneurin. Weiss and Wilkins (1936) described the clinical syndrome of cardiac beriberi associated with alcoholic gastritis, which resembles the classical form of the disease. Alcohol is a significant factor in precipitating beriberi, not only because it supplies calories without B_1, but also because its metabolic effect is similar to that of pure carbohydrate. In response to aneurin the cardiovascular disorders disappear before the polyneuritis. Dysfunction of the cardiovascular system resulting from unbalanced food intake is a disease of regular occurrence in America. Tachycardia, followed by bradycardia, and gallop rhythm with electrocardiographic changes are considered to be characteristic of the beriberic heart.

Strauss thought that the *polyneuritis of pregnancy* may be of the same nature when pernicious vomiting occurs. In *diabetic neuritis* also it has been shown that the injection of aneurin exerts an influence upon carbohydrate metabolism.

Infantile beriberi.—This form is common in Egypt, the Philippine Islands, South China and certain Pacific Islands, and causes a high infantile death-rate. In the Philippines especially it was a terrible scourge, accounting for 16,500 deaths annually, or 28·1 per cent. of total deaths in infants under one year. It is not necessary to regard it as resembling adult beriberi in miniature, for it differs in many essentials. The disease often occurs in the rainy season. It is never seen in Caucasians, rarely in half-castes, and should be regarded as strikingly a disease of poverty. It usually affects breast-fed infants of mothers who are either themselves victims of the disease or subsist on a diet poor in vitamins. In Hong Kong Fehily stated that in initial, subacute and acute infantile beriberi breast-feeding immediately antedates the symptoms, but in the chronic form breast-feeding might have ceased weeks or even months previously. Removing the infant from the breast, or administering an extract of rice bran, usually leads to a rapid cure.

Vedder and his American colleagues believed that the disease depends upon deficiency during uterine life and after birth of a substance in the milk which is essential to the growth and development of the child's nervous system. However, in children who die in this manner no imperfection or lack of development of the nervous system has been noted. In the most acute type it is children previously healthy, 1½ to 3 months old, who are usually attacked; after a series of convulsions the child suddenly dies of acute heart-failure. In less fulminating cases, vomiting, dyspnœa, dysphagia, and aphonia may precede heart-failure. The child moans in characteristic fashion and the beriberic cry is diagnostic. Ptosis is also common. The blood pressure is low. The total acidity and free hydrochloric acid in the gastric juice are reduced. Occasionally, chronic cases are seen in which progressive weakness and wasting, with periodical attacks of vomiting, occur. In neither form has true paralysis been noted, except that underlying aphonia which was ascribed by Japanese workers to a paralysis of the left recurrent laryngeal nerve from pressure by a dilated left auricle. According to Chan, the knee-jerks are usually absent.

Some highly interesting suggestions were made by G. W. Bray on the inhabitants of Nauru in the Pacific. The death-rate from infantile beriberi in that island, amongst breast-fed babies from eight to ten weeks after birth, had been approximately 30 per cent. of the total deaths during twelve years. The mothers themselves showed no signs of dietetic deficiency, though their dietary was singularly deficient in vitamin B_1. Bray was able to demonstrate the almost instantaneous effects of partially-fermented "toddy" (the sap of the coco-nut spathe), not only in cure, but also in prevention. The dosage of "toddy" is half a drachm twice daily during the first month, one drachm twice daily during the second, three times daily from three to six months, and over that age, three to four ounces weekly. In consequence of this simple measure the disease ceased to exist amongst the Nauruans, while the incidence of a variety of other disorders, such as bronchitis, pneumonia, furunculosis and otitis media abated. It appeared that this peculiarly dramatic form of infantile beriberi became prevalent since the use of "toddy" was prohibited by Government order.

Fig. 62.—Infantile beriberi. Nauruan child in convulsions. Note general anasarca. (*Dr. G. W. Bray.*)

Mortality.—The mortality in beriberi varies in different epidemics and in different localities. On the whole, it is greater in low than in high latitudes, in the dropsical than in the atrophic forms, in the acute than in the chronic. In some epidemics it is as high as 80 per cent. of those attacked; in others as low as 6 per cent., or even lower.

Burning Feet.—"Chachaleh" (Somaliland); "Bárasheh."

This is a very chronic condition which has been recognized in Malaya, British Guiana, West Africa, and Somaliland for many years. Buchanan reported on a series of over 100 cases from Somaliland. Pain is usually generalized, but may occur in various localities, particularly the joints, and at the back of the neck and in the shoulders.

In 82 per cent. there was solid œdema of varying degree, whilst there was thickening of the subcutaneous tissues, especially of the thighs, abdomen, and pectoral and deltoid areas in 41 per cent. Epigastric pain is common and constipation the rule. The knee-jerks are diminished in 39 per cent. of cases. In Malaya, Kingsbury noted sixteen cases, all, with one exception, in Southern Indians. The patients complain of severe "burning feet," usually limited to the soles, but occasionally involving the lower part of the legs. In some instances the pain was definitely worse in the mornings and was always intensified by walking. Sometimes there is a definite history of formication. This condition is now considered to be a deficiency disease, probably connected with beriberi, and also to be curable by administration of vitamin B_1. Since Moore, Scott, Landor and Pallister have described neurological symptoms (weakness, ataxia, incoordination and loss of visual and auditory acuity) associated with burning feet, Stannus believes that it is a further manifestation of ariboflavinosis (p. 441).

Diagnosis.—Usually the diagnosis of beriberi is not difficult. Multiple peripheral neuritis occurring as an epidemic, or in a place or ship in which the disease has occurred on some previous occasion may, as a rule, be set down as beriberi. Sporadic cases may be difficult to diagnose, especially if there is a history of alcoholism, of malaria or of drugging with arsenic. The presence, actual or past, of œdema—especially of œdema over the shins—and palpitations and other evidences of cardiac implication, are significant of beriberi. In the atrophic or paralytic type the *jongck* or "*squatting test*" is very useful. The patient is unable to assume, or rise from, a squatting position with his hands on top of his head. It must be borne in mind that slight anæsthesia of the prætibial skin area, slight œdema of the same region, slight hyperæsthesia of the calf muscles, and, perhaps, impairment or absence of knee-jerk may be the only signs. *Rheumatism is rare in the tropics.*

Pyruvic acid determination in the blood is of diagnostic value. In acute beriberi the blood contains about 2 mgm. per cent.; in untreated chronic cases 1·5 mgm. per cent. and in those injected with aneurin about 0·5 mgm.

Meyers introduced two new tests for the diagnosis of beriberi. The first is the development of, or increase in, an audible sound in the ante-cubital space after subcutaneous injection of adrenalin. The second and more important is the estimation of diuresis after the fasting patient has drunk a litre of water. The volume of urine passed every half hour is charted for four hours. A normal person excretes all the fluid, but in beriberi there is water retention; this should disappear after treatment with aneurin. (Volhard's diuresis test.)

Differential diagnosis.—Cases have been diagnosed as cardiac disease, tabes dorsalis, muscular rheumatism, progressive muscular atrophy, ascending spinal paralysis, and have over and over again been relegated to that refuge for ignorance, malaria. There should be no difficulty in distinguishing beriberi from tabes dorsalis, by the Argyll-Robertson pupil and the positive Wassermann reaction. In both paraplegic beriberi and locomotor ataxia, Abadie's sign (absence of pain on compressing the tendo Achillis) is present.

Beriberi can be differentiated from *alcoholic neuritis* by the tremors and mental disturbances which are generally obvious; from *arsenical neuritis* by the pigmentation, the diarrhœa, and digestive disturbances, and by the hyperkeratosis of the palms and feet that is apt to occur in this intoxication; from *chronic lead-poisoning* by the blue line on the gums, the wasting of the arm and leg muscles which are most in use, the characteristic sparing of the supinator longus, and the basophilic stippling of the red blood-corpuscles; from *lathyrism* by the presence of the knee-jerks and the absence of muscular hyperæsthesia in this affection; and from triorthocresyl phosphate poisoning (ginger or jake paralysis) which causes a flaccid form of motor paralysis. The differential diagnosis from heart disease, chronic nephritis, and ancylostomiasis is sufficiently obvious.

It may be necessary to differentiate Korsakoff's syndrome, Landry's paralysis or Wernicke's syndrome.

Schretzenmayr described the radiographic appearances of the beriberi heart. Three stages can be distinguished; of these the second, with special enlargement of the right auricle, is regarded as characteristic of beriberi.

There are probably other forms of polyneuritis distinct from beriberi, which may closely simulate it. Possibly these infectious forms of polyneuritis are occasioned by an organism as yet undetermined. Possibly also, infective forms of polyneuritis occur in association with food-deficiency. These may account for sporadic cases in which pyrexia is prominent, and also for isolated outbreaks not apparently associated with a faulty dietary.

Famine œdema (nutritional œdema) is more pronounced than œdema of simple starvation, and other causes than mere lack of sufficient nutriment are at work. It is most pronounced in the feet and legs, and marked muscular weakness and alimentary-tract disturbance are common. When there was a shortage of fats, as in Central Europe during the 1914-1918 war, ocular manifestations were frequent. In Java and Haiti a form of malnutritional œdema is prevalent among individuals whose diet is inadequate, and amongst infants fed on a preponderantly starchy diet over a long period. In these a generalized dropsy, similar to famine œdema and œdematous beriberi, is observed. Though resembling œdematous beriberi, this condition is probably not due to vitamin deficiency, but to lack of albumin and fats in the food. Blood analysis reveals a deficency in the albumin-content. The condition is curable by a liberal dietary.

Prognosis.—The tendency to dilatation of the heart is the dangerous element in beriberi; it should always dominate treatment. It is wonderful how rapidly it may come on, and how quickly it may prove fatal. Sudden deaths, occurring sometimes from syncope—from instantaneous failure, as well as from the somewhat slower process of increasing over-distension—are constantly found. An absolutely favourable prognosis, therefore, ought never to be ventured, even in the mildest-looking case, nor so long as the patient is exposed to the conditions causing the disease, or the neuritis appears to be active. That is a lesson which is often, and sometimes painfully, borne in upon the practitioner in beriberi districts.

Evidences of grave heart-implication, such as pulsating cervical vessels, equal spacing of the intervals between the sounds audible on auscultation, enlargement of cardiac dullness, especially to the right, epigastric pulsation, a rapid feeble pulse, a distended stomach, cold extremities, cyanosis, dyspnœa, and a disproportion in the strength of the heart- and wrist-beats, are significant of danger. *Paralysis of the diaphragm, of the intercostal muscles, extensive serous effusions and very scanty urine* are also unfavourable signs.

Vomiting.—No one can say when or how soon fatal implication of the cardiac nerves and muscle may take place, but vomiting is always an ugly and threatening symptom. The Japanese regard it as of fatal import. Marked dilatation of the stomach has a similar significance.

Prognosis is improved if the patient is placed on a non-beriberic diet and is treated with full doses of aneurin before the heart-muscle or the cardiac or respiratory nerves are gravely degenerated.

TREATMENT

The first and most important thing is the diet. From this, rice, especially white rice, should be eliminated, and some article rich in vitamins—such as beans, peas, peanuts, barley, wheaten flour (not overmilled), or oatmeal—substituted. Apart from other considerations, rice is a bad food for beriberics ; it is too bulky. Eggs are valuable sources of the anti-beriberi factor, which is not destroyed even when they are dried. Yeast has curative properties ; the extract known as *marmite* may be given in doses of 1·5 grm. daily. Animal food, including fat and milk, must enter into the dietary for general nutritional purposes. The worst cases, particularly if there is any sign of serious cardiac implication, should remain in bed : but the mild cases had better spend the greater part of the day in the open air.

In cardiac cases, with a view to diminishing to some extent the bulk of blood in the vessels and heart, the seriously affected patients should take little fluid, and keep the bowels free by full and repeated doses of some saline aperient. Small doses of digitalis or strophanthus seem to do good. Should signs of acute cardiac distress appear, full doses—3, 4, or 5 drops of the 1 per cent. solution—of nitroglycerin are indicated, and intravenous injections of ouabäine (a French preparation of strophanthin) $\frac{1}{250}$ to $\frac{1}{75}$ gr. may be given. The dose must be repeated every quarter- or half-hour, and kept up until the threatening symptoms pass away. In suddenly developed cardiac attacks, inhalations of nitrite of amyl, pending the operation of nitroglycerin, are useful. Should signs of cardiac distension and failure persist and increase in spite of these means, there must be no hesitation in bleeding the patient, taking, if it will flow, eight or ten ounces from the arm or (this failing for any reason) from the external jugular. Often, as the blood flows, rapid amelioration of the alarming condition sets in, and the patient is, for the time being, tided over an acute danger and given another chance. The bleeding should be repeated if the alarming symptoms recur, as they are almost sure to do. Oxygen inhalations, if available, are worth trying in cardiac attacks. Pleural and pericardial effusions should be sought, and, if deemed to be interfering in the slightest degree with the circulation or respiration, drawn off with the aspirator.

The introduction of vitamin B_1 (aneurin) as a therapeutic agent has entirely revolutionized the treatment of beriberi, and its dramatic effects are best observed in the acute cardiac cases when given in big doses. Hawes, Monteiro and Smith emphasize that it is in the acute attacks which break out without any previous warning that its effects are best seen. Wilkinson recommends immediate intravenous injection of 50 mgm. of aneurin, to be repeated two or three times in twenty-four hours until serial skiagrams show that the heart has become reduced to normal limits. In moribund patients the injection has been made direct into the jugular vein with spectacular success. There are two crystalline preparations in use for injection, *Betaxan* (Bayer) and *Benerva* (Hoffman, La Roche). These preparations normally contain 2 mgm., but the strong or " forte " dose is 10 mgm., of crystalline aneurin per c.c.

preparation "Bemax" is widely used. *Crystovibex* (Parke, Davis & Co.) is aneurin in tablet form, and is issued in two strengths, 333 international units (1 mgm.) or 2,231·2 international units (6·7 mgm.). Benerva and Betaxan are also issued in tablet form for oral administration in doses of 1 mgm. each.

Hawes originally showed that active extracts of vitamin B_1, when given by the mouth, are destroyed in the stomach, but after the injection of a potent extract most striking therapeutic effects are noted. In cardiac or œdematous cases the patient, even when moribund, at first becomes restless after the injection, but no effect is noted in the pulse rate or in the diastolic or systolic pressures for an hour or more. If insufficient vitamin B_1 has been injected, there may be a return of the dyspnœa, sudden collapse and death. In many cases, recovery is extremely dramatic. The dosage varies in different cases. The reaction is quantitative, and the results become apparent in the rise of systolic and diastolic blood-pressures.

In advanced paraplegic cases the results of aneurin treatment are by no means so satisfactory; whereas pain and subjective dysæsthesia are relieved, the nervous signs take a long time to disappear. In the Far East, especially in China, results are disappointing, because patients inevitably relapse when they return home and resume their polished rice dietary.

Breast-fed beriberic infants should be removed from the mother and handed over to a healthy wet-nurse, or placed on the bottle. Sometimes this is impracticable; in such cases in the Philippines a preparation of extract of rice-polishings, known as "tiqui-tiqui," has the reputation of being wonderfully efficacious. It is given to the extent of 5 c.c. a day in 20-drop doses every two hours. At the end of twenty-four hours the most alarming symptoms disappear, and the child is well in three days. If the case is a very severe one, double doses should be given, and the tiqui-tiqui continued so long as there is any aphonia. Under modern conditions obviously aneurin is indicated. How found that in the most acute cases one injection of 5 mgm. aneurin, followed by 3 mgm. by mouth, sufficed. In chronic cases oral administration is satisfactory.

Excretion of aneurin.—The excretion of aneurin in the urine can be estimated, with sufficient accuracy to be of clinical value, by the thiochrome method without the use of the fluorimeter. Rapid excretion takes place in the first three hours after subcutaneous or intramuscular injection. It is suggested that a certain amount of injected aneurin is excreted before there is time for it to be stored in the tissues (Marrack and Hoellering).

Other measures.—For the atrophy of the muscles and anæsthesia of the skin, faradization and massage should be employed as soon as the muscular hyperæsthesia has begun to subside. Hot-air baths are of considerable service. Care should be taken that permanent deformity does not occur from contraction of muscles. Foot-drop should be counteracted by Phelps's talipes splint with an elastic accumulator, and any other threatened deformity appropriately met. Relapses must not be risked by a return to the original diet.

Prophylaxis.—In institutions under Government control, or in conditions in which it can be successfully enforced, there should be a stringent rule against the use of overmilled rice. To legislate against the use of

CHAPTER XXV

PELLAGRA

Synonyms.—Mal de la Rosa; Mal Rosso; Alpine Scurvy; Asturian Rose.

Definition and description.—An endemic disease of slow evolution, which is undoubtedly connected with dietetic deficiencies, characterized by a complexity of nervous, alimentary and cutaneous symptoms, which make their first appearance during the spring months (sometimes the autumn), and recur year after year at the same season, remitting more or less during the winter months. It is for the most part confined to the poorer classes, especially agricultural labourers. The more distinctive features are (*a*) a remitting dermatitis of the exposed parts of the body; (*b*) marked emaciation; (*c*) profound depression alternating with mania; (*d*) a terminal confusional insanity.

History.—The history of pellagra is comparatively recent. In Spain it was first described by Casal in 1763, under the name of *mal de la rosa*. In Italy the disease, under the name of *Scorbuto alpino*, was described by Odoardi in 1776 and by Frapolli in 1771. The earliest mention of pellagra in France dates from 1829. We know nothing of the history of pellagra in Egypt before the publication of Pruner's "Topographie médicale du Caire," in 1847. In the United States of America, although there is evidence of its sporadic occurrence there for at least fifty years, before its nature was recognized, pellagra was first diagnosed as such in 1907. It is especially prevalent in the South-Eastern States. Dr. H. F. Harris, Health Officer of the Georgia State Board of Health, estimated that there were 50,000 cases of pellagra in his State, and in 1916 there were 150,000 pellagrins in the Southern United States alone, though during recent years the American outbreak has become milder.

Since 1912 sporadic cases of the disease have been reported in the British Isles. Many of these fall into the category of what is known as "secondary pellagra."[1]

Geographical distribution.—*Europe*: Pellagra is found in Northern Portugal, in Spain, in Italy, in the south-west of France, sparingly in Denmark and in the British Isles, in the Austrian Tyrol, in Hungary, Croatia, Dalmatia, Bosnia, Jugoslavia, Bulgaria, Turkey, Greece, Corfu, Roumania, Bessarabia, Kherson, Poland and Transcaucasia. A few cases have been reported from Germany. *Africa*: Algeria, Tunis, Egypt, Sudan, the Red Sea coast, Rhodesia, Nyasaland, and among the Kaffirs and Zulus. It has also been recognized in Tanganyika, Kenya and on the Gold Coast. *Asia*: It has been reported from Asia Minor, Armenia, Syria, North Behar and Deccan in India, the Malay States, the Philippine Islands, Japan, China and Korea. An outbreak of pellagra was recorded in Nanking in 1920, in Shanghai in 1940, and by French observers in Szechuan. Yu reported typical cases in Manchuria. It was especially prevalent among Turkish troops and Armenian refugees in Palestine and Syria during the 1914-18 war. *America*: Canada (since 1914), the United States, Mexico,

---

[1] For more detailed information the reader is referred to the masterly summary by H. S. Stannus in the *Tropical Diseases Bulletin*, **33**, 10–12, and **34**, 3.

Central America, Brazil, the Argentine, Barbados, Jamaica, and probably other West India Islands. *Australasia:* Pellagra has been reported from New Caledonia and in Australia (Melbourne).

Pellagra in Great Britain.—According to Stannus, the first authentic case in Great Britain was reported by Howden in 1866, the second by Brown in 1906, and the third by Brown and Low from Shetland in 1909. In 1912 a series of six cases was investigated by Sambon and Chalmers, and in 1913 Box published his two famous cases in St. Thomas' Hospital. Since then it has come to be generally recognized that pellagra is found sporadically in lunatic asylums and other institutions, in subjects of general malnutrition. In the statistics of the Board of Control in the period 1913–1918, 45 deaths were noted. In 1922 there were 21 deaths, mostly from the Lancashire Mental Hospital, Rainhill, and during the period 1913–1928 there were 104 deaths from pellagra amongst asylum inmates.

Epidemiology and endemiology.—An important epidemiological feature of pellagra is the marked fluctuation of its prevalence from year to year. Thus, there may be long periods of quiescence, followed by years of considerable activity during which the disease may be looked upon as a new invasion. There is no evidence that pellagra is spread by contagion. The sound may associate with the sick and remain healthy. Doctors, nurses, and attendants on pellagrins are not known to contract the disease. Pellagrous wet-nurses do not infect their charges.

Associated diseases, such as ancylostomiasis, bilharziasis, malaria, tuberculosis, cœliac disease, idiopathic steatorrhœa, sprue, chronic bacillary dysentery and syphilis, play a very important part in favouring the development of pellagra, in accelerating its course, in modifying and aggravating its symptoms, and in determining its mode of termination.

Season.—Of all diseases with marked seasonal connection, pellagra is one of the most striking. The pellagra season varies in different localities, but is always the same in the same locality.

In Europe the disease invariably appears in manifest and epidemic form during the spring and autumn quarters, the spring outbreaks being by far the more severe, the autumnal recurrence often inconspicuous or lacking. In Egypt, according to Chalmers, there is a spring invasion in April and May, and an autumn recurrence in November. In Nyasaland, according to Stannus, pellagra seems to prevail chiefly during August, September, and October, which are the spring months in the southern hemisphere, and again, though to a lesser extent, in January, February, and March (fall recurrence). In the United States of America, owing to the vast extent of territory and great variety of climates, the periodical incidence of the disease is necessarily different in different sections. In the Northern States, as in Europe, the disease exhibits the usual well-marked double incidence, the spring outbreak occurring in May and June, the autumnal one in September and October. In the far south the disease may appear as early as January, and may be met at any period of the year. In Barbados it seems to prevail more or less from May to October or November. While the wide range of pellagra throughout the world might suggest that climate exerts no special influence, the very definite seasonal periodicity shows that climatic factors play an important, though indirect, part.

Sex.—Both sexes are liable, but in different places the disease exhibits a very different predilection for the one or other sex in accordance with the occupations and habits of the people. In the United States it is said to be more prevalent in women from 17 to 40 years of age; the debilitating effects of menstruation, pregnancy, and lactation are held to be predisposing and determining factors.

Age.—Pellagra is a disease of middle age, the majority of cases occurring between twenty and fifty. Within the endemic centres children are attacked, and infantile pellagra is common in West and East Africa and Southern China (*see* p. 441).

Occupation.—The disease prevails most of all among field-labourers. The inhabitants of towns, even of those in the very heart of intensely pellagrous districts, usually enjoy immunity. Although it has been stated that pellagra is rare in the Jewish race, it is quite common in Palestine, where it is confined to the poor town dwellers, whilst agricultural labourers for the most part escape.

The flooding of some of the Southern States in America by the overflowing of the Mississippi in 1927 afforded a practical example of the dietary factor. Pellagra, though common in these States, depends to a great extent on economic conditions. The diet of molasses and cornmeal contains very little of the PP factor, and only when the financial conditions allow can milk, eggs, etc., be purchased. The failure of the cotton crop meant poverty, reduced food, and pellagra.

Ætiology.—Pellagra was formerly ascribed to the most varied causes, such as insolation, poverty, insanitary dwellings, syphilis, irritant oils, bad weather, alcohol, garlic, onions, maize. Some regarded it as "sunstroke of the skin." "Sun disease" was an old popular name, and certainly the skin manifestations of pellagra are influenced by the action of the direct rays of the sun: This was proved experimentally, first by Gherardini, who varied the limits of the eruption by systematically displacing parts of the clothing; and later by Hameau, who obtained differently shaped patches of erythema by means of gloves fenestrated in different ways. In smallpox, and also in other exanthemata, light has a decided influence, more particularly the actinic rays, on the production of skin eruptions. Although light may influence the eruption in pellagra, this is no adequate reason for concluding that insolation is the cause of the disease, any more than that it is the cause of smallpox, and in fact other stimuli applied to the skin, such as pressure or exposure to X-rays, may cause the appearance of a pellagrous dermatitis.

Pellagra and maize.—The general opinion was that pellagra appeared soon after the introduction of maize into Europe, and that it advanced *pari passu* with the extension of maize cultivation and with the more general adoption of the new cereal as an article of food. For these and other reasons maize was held by many to be the causative agent of pellagra, just as a certain condition of rye was known to be the cause of ergotism; and, as in the latter case, various theories have been propounded to explain the operation of the assumed cause.

Lombroso and Bellardini, in 1871, first advanced the theory that the prevalence of pellagra in Italy was due to the consumption of diseased maize, and their ideas subsequently formed the basis for public measures against the disease in that country, as well as in Southern Europe. In Lower Egypt, as pointed out by Wilson, pellagra is common, as compared to Upper Egypt, and it is in the Delta that the proportion of land given over to maize is considerably higher than that under wheat, so the distribution of pellagra in that country corresponds to the area of maize cultivation.

Deeks in 1912, and Funk in the same year, suggested that pellagra was a disease produced by a deficiency in diet. In 1914 Goldberger and Wheeler fed a squad of eleven prisoners on a rich carbohydrate diet deficient in proteins. After five months, six developed cutaneous symptoms suggestive of pellagra (the first lesions consisted of an erythematous patch on the scrotum). An experiment in the converse direction also proved successful, for, by substituting a rich protein diet for one consisting in great part of carbohydrates, they succeeded in banishing pellagra from an orphanage asylum in which up to that time pellagra had been in evidence. In 1917 Goldberger successfully disposed of the "infection theory" by obtaining sixteen volunteers who attempted to infect themselves by ingesting skin scales and naso-pharyngeal secretions of pellagrins over a period of six months. They remained quite healthy. In 1919 the commission which investigated the prevalence of pellagra amongst the Turkish prisoners in Egypt attributed the cause to a primary deficiency of "biological proteins" (B.P.V. = Biological protein value).

The Vitamin B_2 Complex.—Goldberger, who at first believed that an amino-acid deficiency was the cause of pellagra, in 1922 obtained evidence pointing in another direction. Having discovered that yeast was effective in preventing and curing blacktongue in dogs, generally considered to be analogous to pellagra, Goldberger and Tanner tried the effect of yeast as a prophylactic in the human disease, and found that 30 grm. daily of brewers' yeast gave complete protection. This would supply less than 15 grm. protein, and later it was found that an acid preparation of yeast, which contained very little protein-nitrogen, in doses of 15 grm. daily, was equally effective. A PP (pellagra-preventive) factor was therefore postulated in yeast and other foodstuffs. As the result of these investigations on man and experimental work on rats, Goldberger and his colleagues were able to identify the PP factor with a vitamin in the yeast-vitamin complex differing from aneurin in its stability to heat and its distribution in foodstuffs.

It was subsequently discovered that the PP factor was in fact composed of elements of the vitamin B complex the chief constituent of which was nicotinic acid or nicotinamide. Modern opinion is that riboflavin (the typical vitamin B_2) is concerned in the genesis of several of the more prominent pellagrous lesions. "Ariboflavinosis" is quite distinctive and has been well described by Sydenstricker.

Liver and meat contain a high proportion of nicotinic acid and this explains the well-ascertained fact that these substances are effective in the treatment of pellagra in man, as well as of blacktongue in dogs. Nicotinic acid and riboflavin have been found to be efficacious in the treatment of pellagra (*see* p. 443).

Although there can be no doubt that deficiency of nicotinic acid causes pellagra, the relation of the disease to the amount of this vitamin in food and the association of pellagra with maize is not yet quite clear. Maize contains less nicotinic acid (1–1·6 mgm. per 100 grm.) than wheat (4 mgm.), but more than rye, millet and refined flour. It is possible that the nicotinic acid in maize is, in some ways, unavailable.

The not infrequent occurrence of *secondary pellagra* is probably due to non-absorption of the necessary vitamins by a diseased or non-functioning mucosa.

Pathology.—The pathological features essential to pellagra may be obscured by complicating diseases, such as bacillary dysentery and tuberculosis. The morbid anatomy is neither constant nor characteristic; for this the chronicity of the disease, the variety of the symptoms, and the many intercurrent affections which may arise are responsible.

A constant and striking feature is the great emaciation. The viscera show chronic degenerative changes, particularly fatty degeneration, and a characteristic deep pigmentation. The intestinal walls are greatly attenuated through wasting

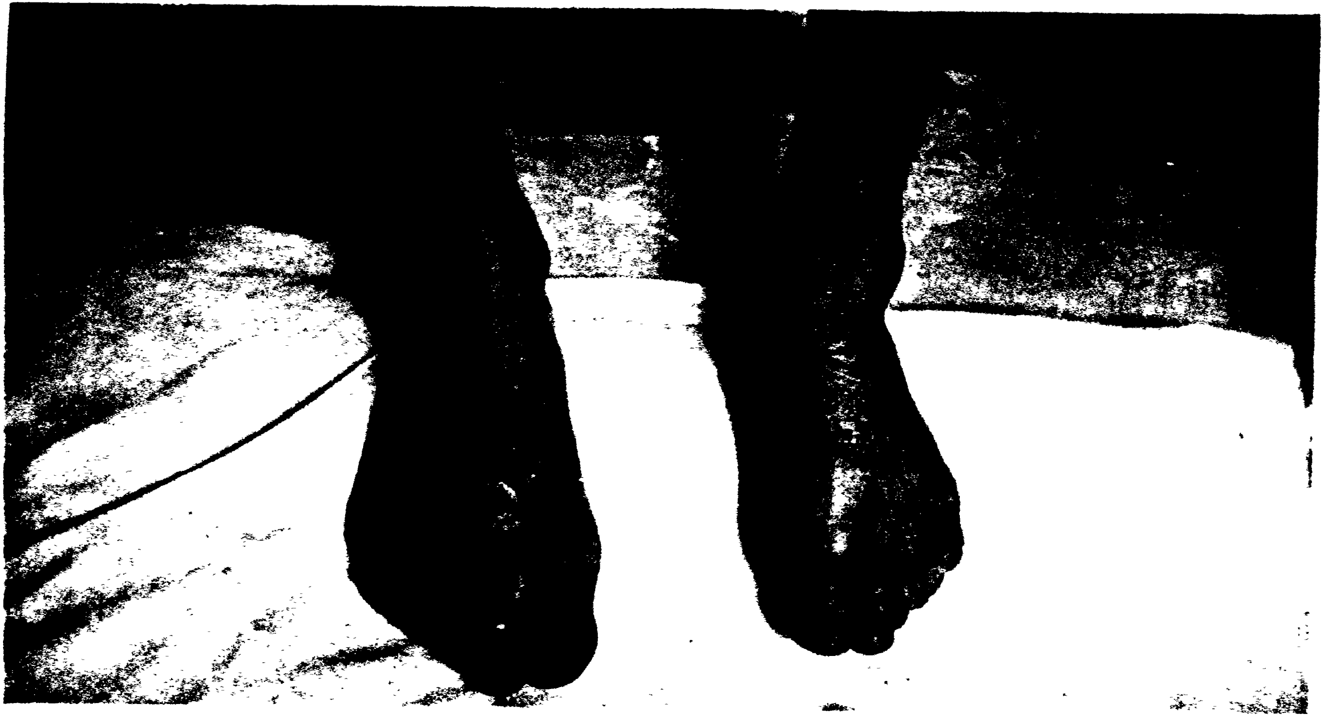


Photo: Dr. A. D. Bigland.

PELLAGRA RASH ON FEET.

Dorsa of feet had been exposed to sun in area between turned-up trousers and uppers of shoes.

Plate VIII

of their muscular coat, while at the same time the mucous lining is hyperæmic and, not infrequently, ulcerated. The liver and spleen are usually atrophied. The suprarenal capsules may be atrophied and the cortex may be black, while the medulla is whitish and may be the seat of hæmorrhages. The heart is usually in a condition of brown atrophy and weighs only 2–3 ounces.

There may be wasting of the brain, the ventricles being distended by an excess of fluid. In the cord the lateral columns and the crossed pyramidal tract are especially implicated, but the direct cerebellar tracts usually escape. The interior cornual cells are frequently atrophied and deeply pigmented. The posterior columns do not escape, the median portion often being degenerated. The degenerative changes in the lateral columns are chiefly in the middle and lower thirds of the dorsal region, those of the posterior columns principally in the cervical and upper dorsal region. The cerebro-spinal fluid shows little change; there is usually no increase in the globulins.

Mott remarked on the changes in the cerebrum, cerebellum, pons, medulla, and spinal cord that in none of the sections is there any evidence of meningeal or perivascular infiltration with lymphocytes, plasma cells, or polymorphonuclear leucocytes. All the changes were like those produced by a chronic toxæmia, possibly in the manner already suggested. The posterior spinal ganglia cells show, in varying degree, a pronounced chromatolysis, swelling of cells, and disappearance of Nissl's granules, and all the anterior-horn cells and their homologues in the medulla and pons a varying degree of perinuclear chromatolysis. With the Marchi method, degeneration is most definite in the column of Goll. In most cases the afferent tracts are more affected than the efferent. There is usually marked chromatolysis of the cells of Clarke's columns. The Betz cells of the cortex and the cells of Purkinje showed similar changes, but in a lesser degree. In short, the changes in the central nervous system resemble those of central neuritis (Adolf Meyer) or of subacute combined degeneration of the cord.

Shattuck drew attention to the close ætiological relationship between beriberi, Korsakoff's syndrome, pellagra, central neuritis, and subacute combined degeneration of the cord.

Central neuritis, which is undoubtedly allied to pellagra, was first described by H. H. Scott on sugar estates in Jamaica, and it was subsequently found in Sierra Leone and Nigeria. The central nervous lesions are widespread; the peripheral nerves are demyelinated and the posterior root ganglia of the spinal cord show degenerative changes. The medulla, cerebellum, basal ganglia and optic nerves are also affected.

Clinical pathology.—There is hypochlorhydria in 40 per cent., and quite frequently achlorhydria. In advanced pellagra there is usually anæmia, which is of macrocytic and hyperchromic type in about 50 per cent.: microcytic in the other half. The total leucocyte count is not disturbed, though there is often lymphocytosis. An indirect van den Bergh reaction is usually present in the serum. There is no change in the corpuscular fragility; the plasma albumin is diminished.

The fæces are pale, foul, milky, soapy, sometimes steatorrhœic. The urine is generally alkaline and may rapidly become ammoniacal. It may also contain tube-casts, traces of albumin and, usually, indican. Much attention has recently been drawn to the excretion of coproporphyrin (porphyrinuria) and speculations have been made regarding its significance. Some regard it as indicating faulty liver metabolism; others as the result of abnormal intestinal absorption. As stated by Beckh and Ellinger, it is specially found in secondary alcoholic pellagra, but Spies, Cooper and

Blankenhorn showed that the amount of coproporphyrin in the urine appears to be proportional to the nicotinic acid intake.

Symptoms.—The cardinal signs of pellagra constitute the well-known diagnostic triad : " diarrhœa, dermatitis and dementia." The course is generally long and irregular, one of repeated exacerbations and periods of quiescence. The initial symptoms are composed of mingled psychical and digestive disturbances which may recur for years without the appearance of skin eruptions. The patient is pale, has a peculiar lifeless staring look, with dilated pupils, and complains of headache, giddiness, and vague but often severe pains in the back and joints. The scleræ are bluish and leaden coloured. The eyelids move sluggishly ; the complexion is muddy. The character changes, becoming irritable, and at the same time stupid and morose.

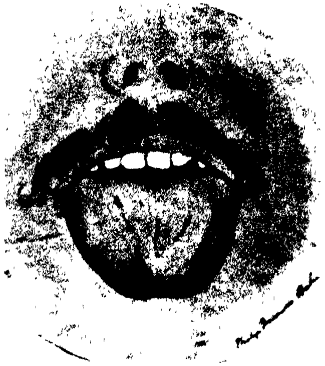
Observations on children in pellagrous families in the United States show that many have clinical signs of pellagra. They are below the normal weight and height for their years, they make slow progress at school, show lack of interest, inability to concentrate and have poor appetites. Their hearts are irritable and they may have tachycardia.

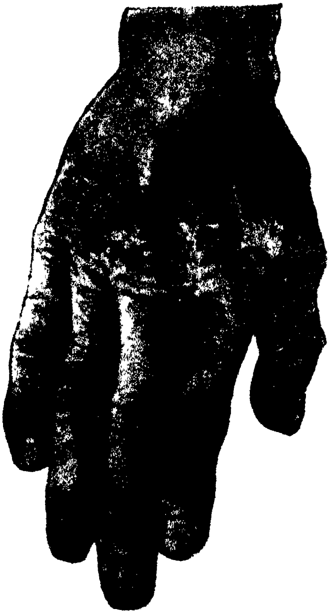
The earliest signs of a pellagrous tendency are difficult to define, as there are probably a great many people who suffer from chronic ill-health and are really in the pre-pellagrous state. This tendency may manifest itself by a peculiar stomatitis with erosions at the angles of the mouth (angular stomatitis) (Plate IX).[1] There may also be an atrophic condition of the lips (*perlèche*) to which the Editor drew attention in Ceylon in 1912 in prisoners who had been fed on dried fish (*see* p. 539). The pellagrous process may not proceed beyond this stage. On the other hand, it may be progressive and advance to a fully developed syndrome. Then the gums may be swollen and bleed easily, a condition which gave rise to the term " Alpine scurvy." There may be eructations of gas, nausea, and vomiting. The appetite is variable. The epigastric region and, sometimes, the lower abdomen are tense and painful. Constipation may be present, but in rare instances there is diarrhœa of pale fermenting stools resembling those of sprue.

The pellagrous rash.—Most observers regard the skin lesions of pellagra as early manifestations, but they are symptomatic of the underlying constitutional disturbances. At first an erythema, not unlike a severe sunburn, is observable on the parts of the body which are, as a rule, unclothed and exposed to the sun (Plates VIII, IX). The eruption is symmetrical and characteristic. It appears suddenly, first on the back of the hands and feet, then on the forearms, legs, chest, neck, face, and, it may be, on the scrotum or on female genitalia, anus and other regions subject to mechanical irritation. Patches of erythema are irregular in outline and intensity. Very characteristic is a symmetrical eruption behind the mastoid processes, a ring or collar round the neck (Casal's necklace), and a butterfly patch over the bridge of the nose resembling lupus erythematosus. The affected area is swollen and tense, and the seat of burning or itching sensations which become particularly acute on exposure to the sun. The congestion disappears completely, but temporarily, on pressure. Petechiæ are common on the affected parts ; blebs with clear, opaque, or blood-stained contents of

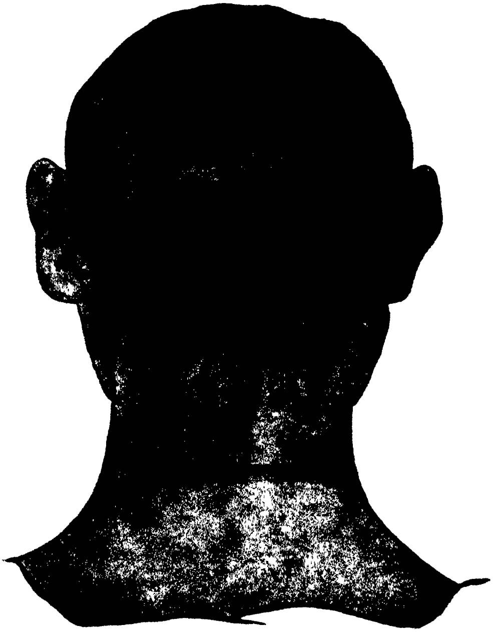
---

[1] Plummer-Vinson syndrome, p. 441.





2



3

Fig. 1. Characteristic inflamed tongue of acute pellagra with angular stomatitis.

Fig. 2. Early pellagrous rash, with cellular infiltration and pigmentation.

Fig. 3. Typical pellagrous rash over occiput and mastoid processes, with formation of "rosary" round neck.

PELLAGRA.

PLATE IX

Fig. 3. (P. H. M.-B.)

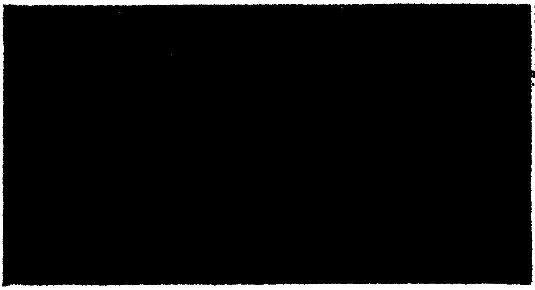


Fig. 2.

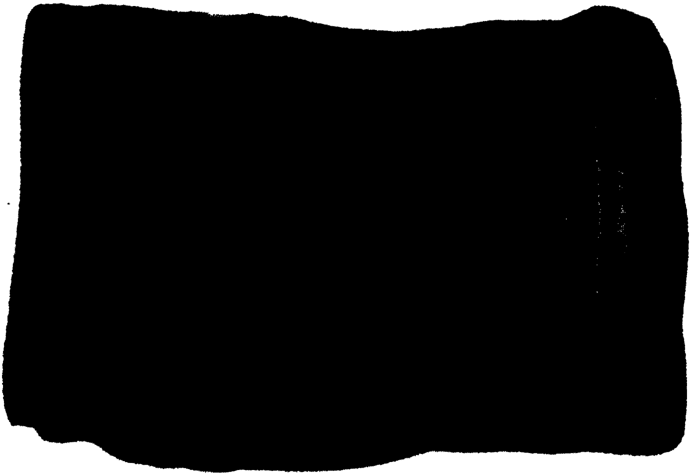


Fig. 1.—AMŒBIC DYSENTERY. Typical patches of infiltration and ulceration of ascending colon, showing "Dyak-hair" sloughs. Fig. 2.—BACILLARY DYSENTERY (Sonne infection): Acute Sonne dysentery in a child, showing bright pink hyperæmia of muscular coat. Fig. 3.—BACILLARY DYSENTERY (Shiga infection): Coagulation necrosis of lower portion of ileum, showing characteristic green coloration of the destroyed mucous membrane.

◆

INTESTINAL LESIONS IN AMŒBIC AND BACILLARY DYSENTERY (*Half nat. size*).

feebly alkaline reaction may form. The eruption usually lasts about a fortnight, and is followed by hyperkeratosis and desquamation, which leaves the skin rough, thickened, and permanently stained a light sepia. This is especially marked on the back of the hands and on the elbows, thus constituting recognizable evidence of pellagra. Hyperkeratosis may occur on the soles of the feet and as diffuse thickening over the knuckles. In severe cases the skin over a large area of the body comes to resemble that of a roasted turkey. Ichthyotic changes sometimes supervene and may be more intense in winter than in summer. It is on account of this roughness of the skin that the disease was originally called " pellagra " (an Italian word derived from *pelle* (skin) and *agra* (rough)).

Stannus has suggested, as a result of the work of Lewis on the blood-vessels of the human skin and their responses, that the skin lesions in pellagra are due to the liberation of histamine and its action upon the blood-vessels, and that the mechanism underlying the affections of the mucous membranes is of a similar nature.

Exposure to light appears to be the precipitating factor. Ruffin and Smith showed that radiation may evoke not only skin lesions, but also associated oral, gastro-intestinal and neurological manifestations. Since injections of porphyrin can sensitize normal persons to sunlight, it has been suggested that there may be abnormal porphyrin metabolism in pellagra. The burning sensation in the soles of the feet and palms of the hands which is such a common symptom in pellagra may be ascribed to the same cause.

Naturally, the appearances of pellagra differ considerably in different races. What is an erythema in the European becomes a blackish or purplish patch on the skin of a negro. In olive-skinned races pellagrous patches assume a sepia colour.

Implication of the *nervous system* is indicated by tremor of the tongue, exaggerated deep reflexes, and mid-dorsal spinal tenderness. Coarse tremors of the extremities, especially of the head and the hands, are frequently noted and become more marked as the disease progresses. Muscular cramps may occur ; definite ankle clonus, spasticity and extensor-plantar response are often seen. The patient suffers from obstinate sleeplessness, occasionally from uncontrollable sleepiness. He experiences great weakness, especially in the lower extremities, and is subject to peculiar attacks of giddiness, with a tendency to fall forwards or backwards. Chvostek's sign—mechanical irritability of the facial nerves—is present in the majority of cases. A very characteristic symptom is pyrosis, or a burning sensation down the œsophagus (dysphagia). This frequently creates the idea in the patient's mind that his food does not agree with him, or even that attempts are being made to poison him. The pupils are dilated and there is usually photophobia. The arms may be spastic and movements are accompanied by a coarse tremor, which is increased on exertion.

After the disappearance of the eruption, atrophic patches of skin remain in the interdigital clefts, and these, together with muscular wasting, give the appearance of washerwomen's fingers. The hands, in fact, are aged out of proportion to the rest of the body. The nails become atrophied and brittle.

As a rule, there is no marked permanent elevation of temperature, but periods of slight fever occur at irregular intervals.

Progress.—Two or three months after onset the symptoms abate and, although the affected skin areas remain dark and rough, the disease appears to be arrested. Next spring, however, the whole series of phenomena recurs in a more severe form. The eruption assumes a darker colour. The depression of spirits deepens into melancholia, which may have maniacal interludes, with a peculiar tendency to suicide, especially by drowning. The general feeling of weakness increases ; the patient loses weight and is unable to work ; his gait becomes uncertain and somewhat of the spastic paraplegic type. The tongue is tremulous. The pains in the head and back become very acute, and there may be lightning pains, cramps, twitchings, tremors, and even epileptiform seizures of the cortical type. Diarrhœa may now be troublesome.

For several years the disease may thus recur in the spring with increasing severity. The patient becomes greatly emaciated, paralytic, and completely demented. Helpless, bedridden, suffering from incontinence of urine and uncontrollable diarrhœa, covered with bedsores, and neglected, he dies from exhaustion or from some intercurrent disease.

The duration of pellagra is exceedingly variable. It may last only two or three years ; it usually extends to ten, fifteen, or more.

Cases differ considerably. The obscure forms are probably much more common than the fully declared disease. They were formerly known—somewhat incongruously—as *pellagra sine pellagra*.

Ariboflavinosis.—The riboflavin deficiency syndrome is now regarded as typical of "*pellagra sine pellagra.*" The following signs are characteristic of it : angular stomatitis[1] and facial lesions consisting of filiform seborrhœic excrescences (dyssebacia), varying in length up to 1 mm., sparsely scattered over the face. The mouths of the sebaceous glands are plugged with inspissated sebum, giving the skin a roughened appearance, which on the shoulder, arms and legs is known as *phrynoderma* or toad's skin. The eyelids show dermatitis lesions, may be macerated and stuck together. Fissures and maceration at the angles of the mouth are seen, and a degenerative crust-like formation on the epithelium of the lips, most marked on the lower. The lips, particularly the lower, frequently show a marked increase in the ver- [illegible] scribed : the tongue is clean, the

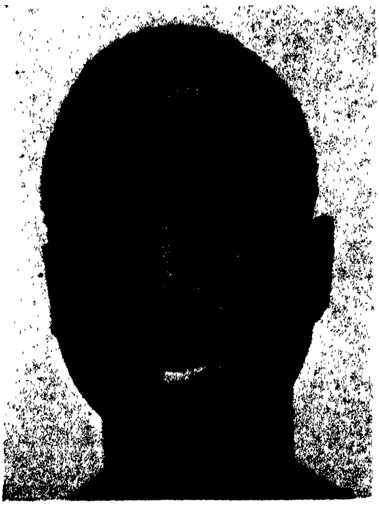


Fig. 63.—Avitaminosis B_2 in a West African negro. Characteristic facies of ariboflavinosis. (*Dr. D. Fitzgerald Moore.*)

---

[1] The term "cheilosis," applied by some writers to lesions at the angles of the mouth, should be reserved for lesions on the lips.

papillæ flattened or mushroom-shaped and the colour definitely purplish red or magenta, in contrast to the scarlet tongue of nicotinic acid deficiency. (Plate XVII.)

The ocular manifestations are burning, lachrymation, photophobia, blurred vision, inability to see in a dim light and visual fatigue. The earliest and most common sign is circumcorneal injection and, when viewed by a slit lamp, there is marked congestion and proliferation of the limbic plexus, with the production of great numbers of narrow capillary loops. The lesion progresses to vascularization of the cornea within a week, if treatment with riboflavin is not given. Eventually keratitis is produced, similar to that associated with acne rosacea, which is also amenable to riboflavin therapy. It is probable that ariboflavinosis is also responsible for retrobulbar neuritis, which may also be part of the pellagra syndrome (*see* p. 408).

Other less marked varieties (*Formes frustes*).—Corkhill and others have pointed out that there are quite a number of subclinical cases in which physical signs are less obvious, but symptoms appear only after undue fatigue.

In some the nervous symptoms predominate, in others the gastro-intestinal; in others again the cutaneous. Forms of hyperæsthesia may occur in different regions of the body, especially the feet (p. 427). Ocular symptoms, such as ptosis, diplopia, retrobulbar neuritis, amblyopia, mydriasis, are not uncommon. The Plummer-Vinson syndrome of glossitis and dysphagia, with angular stomatitis, koilonychia and anæmia, in aged women is possibly a pellagrous manifestation.

Infantile pellagra.—Pellagra in childhood is very apt to be overlooked, especially in native races. The children become irritable, their skin and hair tend to lose the normal colour and glossiness, and there may be attacks of diarrhœa with transient œdema of the hands, feet, and face. After ten days or so pigmented patches appear on the skin of the extensor surfaces about the ankes, knees, wrists and elbows, and these blackened patches appear first where there is any focus of irritation or pressure. Trowell described infantile pellagra in E. Africa as a syndrome of which the principal signs are œdema, dermatitis and diarrhœa; similar cases from W. Africa were described by Williams as "kwashiorkor." This is an acute form with nutritional œdema and decreased serum albumin. Infantile pellagra has also been reported in American negroes, from Mexico, Cuba, Costa Rica and S. China.

Pellagra typhus.—In this very acute type there are intense prostration, high temperature, muttering delirium, pronounced nervous tremor, generalized rigidity, and convulsions. In extensive outbreaks of pellagra, such as occurred among the Turks during the 1914–1918 war, cases of this description were comparatively common.

Terminal stages, pellagrous insanity:—Mental symptoms supervene in one-third to one-quarter of all cases.

It has been estimated that from 4 to 10 per cent. become permanently insane. In the United States of America pellagrins are becoming numerous in the lunatic asylums. The type of insanity is usually a most profound melancholia with a suicidal tendency; cases may resemble in their clinical features general paralysis of the insane. Epileptiform convulsions may occur.

The time of the appearance of mental symptoms is subject to the widest variation. They may be primary symptoms, or occur during convalescence. The mental aberrations may be characterized by profound dementia, hallucinations, and katatonia. As a rule, restlessness, vertigo and insomnia anticipate the characteristic melancholia. In general, the patients exhibit anxiety neurosis with depressive features. Pyschosensory disturbances are common, with intolerance of bright light, colours and noises. The patients are fidgety, quarrelsome and irritable. In spite of increased motor drive, they complain of weakness and fatigue.

Not only may pellagra lead to insanity, but those insane from other causes are very liable to pellagrous manifestations. Goldberger found that in certain asylums in the United States the number of lunatics developing pellagra each year was a constant proportion of the total. In England, pellagra has been noted in lunatic asylums since 1913. Watson, in a review of the pellagra cases in the Rainhill Asylum, Lancashire, found that at the time of onset they had been resident from six months to several years.

Secondary pellagra.—Pellagra due to voluntary restrictions of diet has been recognized by several observers during recent years. Mook and Weiss described the typical clinical picture of pellagra in a young woman on a slimming diet ; Mumford, Carley and others found it in mature women who, for some faddist cult, had been subsisting on an unbalanced dietary ; Guthrie, Green, Walker and Wheeler reported similar phenomena in patients on a ketogenic régime.

Pellagra in all its varied manifestations may be associated with some organic lesion in the gastro-intestinal tract, such as œsophageal stricture, carcinoma of the stomach, pyloric ulcer, pyloric stenosis, carcinoma of the ileum, stricture of the rectum, rectal polyposis, suppurating hydatid cyst, chronic amœbic dysentery, cœliac disease, or idiopathic steatorrhœa ; the Editor recorded one case in association with sprue. When the avitaminosis follows surgical operations, such as partial colectomy, on the gastro-intestinal tract or elsewhere, it is known as *surgical pellagra*. *Alcoholic pellagra* is applied by American observers to the disease in chronic alcoholics, especially those who drink methyl alcohol. It has been suggested by Stannus, by way of explanation, that gastritis is the one common factor which supports the hypothesis that, primarily, in pellagra the fault may lie in the intrinsic factor of the gastric juice.

Diagnosis.—Doubtful cases are occasionally encountered, but localized erythema associated with nervous, particularly mental, symptoms, great debility, and seasonal recurrence, in a person in or coming from a pellagrous district, can hardly be confounded with any other disease. The rash may be mistaken for acrodynia, erythema multiforme, dermatitis venenata, eczema solare, trade dermatitis, lupus erythematosus, syphilis, or poison-ivy dermatitis. " Crazy pavement " skin lesions, which are common on the legs of ill-conditioned natives, are not necessarily pellagrous. The gastro-intestinal disturbance and glossitis have to be distinguished from sprue ; while the nervous manifestations have to be differentiated from hysteria, cerebral syphilis, general paralysis of the insane, ergotism, and lathyrism. In old people with arterio-sclerotic changes and accompanying mental symptoms, there may be lesions of hands and feet which may be a source of confusion. "Pink disease" in children may also be mistaken for pellagra, as the distribution of the skin lesions is very similar.

Treatment.—After the end of the 1914–1918 war and the formulation of the *biological protein theory*, many workers, notably Goldberger and Wheeler, noted that improvement in the pellagrous lesions, and even in the nervous involvement, followed a liberal dietary rich in proteins and in vitamins. Then ensued a period in which liver and yeast extracts, notably marmite, were given an extensive trial, but it was generally conceded that, though the therapeutic secret was locked up in the vitamin-B complex, vitamin B_1 was not the main factor.

In 1937 Elvehjem, Madden, Strong, and Wooley reported the cure of black-tongue in dogs by the administration of nicotinamide prepared from yeast. Shortly afterwards Spies, Cooper, and Blankenhorn recorded the successful treatment of human pellagra cases. These patients were in hospital and received a controlled basal diet, upon which alone symptoms had shown no improvement. Relatively large doses of *nicotinic acid* were given—40–80 mgm. by injection, or 200–1,500 mgm. by the mouth within a period of twenty-four hours. Almost simultaneously, Fouts, Helmer, Lepkovsky, and Jukes reported the cure of four cases of "alcoholic pellagra" treated on the same lines, there being improvement in the mental condition, stomatitis, and the intestinal disorders, as well as cure of the dermatitis. Spies, Bean, and Stone (1938) then published a series of 73 cases of endemic pellagra and 99 of "subclinical pellagra", and stated that they had not observed a single acute case that had not responded promptly to nicotinic-acid therapy. Also, in a special study by Spies, Aring, Gelperin, and Stone of 60 cases showing acute mental disorder, improvement was observed within periods of ten hours to six days after nicotinic acid medication, the daily dosage being 500–1,000 mgm. by mouth, or 100 mgm. intravenously. Further confirmation soon came from Matthews, who studied 13 cases of classical endemic pellagra maintained on a pellagra dietary. These favourable results in American pellagra have received a considerable degree of confirmation in the hands of Alport, Ghaligoungui, and Hanna in Egypt, and also of Ellinger, Hassan, and Taha (1937). They treated 15 cases with nicotinamide (Merck), the dose being 1 grm. daily by the mouth or 0·5 grm. by subcutaneous injection. On the whole, they found that acute inflammation of the tongue and ulceration of the mouth subsided in five to seven days, and the sense of taste returned in the same time; in one case colic supervened almost immediately, suggesting intolerance. Thus nicotinamide effected great improvement in the acute mucous membrane lesions, as well as in the skin condition; on the other hand, chronic skin lesions, friction areas and chronic changes in the tongue were only slightly affected. The appetite, mental condition and general physical health were all improved. Grant and Spies recorded that ptyalism, Vincent's infection and coproporphyrinuria disappeared, and Hawksley found great change in the follicular hyperkeratosis on and around the naso-labial folds.

Since the discovery of ariboflavinosis as part of the pellagra syndrome most authorities reinforce treatment with riboflavin tablets in doses of 1–3 mgm. daily. During the recent outbreak of pellagra in Hong Kong Wilkinson found the effects of intravenous nicotinamide injections almost dramatic. Patients who were disorientated, rambling in speech and unable to co-operate or swallow, became hungry and rational within 72 hours. (In acute pellagra the blood nicotinic acid was found to be 0·31 mgm. per cent. and to rise on treatment to 0·55 mgm. per cent.). In cases with rapidly increasing reduction of visual acuity, associated with concentric constriction of fields of vision, response to nicotinic acid and riboflavin daily changed the vision from 6/60 to 6/9 or 6/6 within a week.

The evidence that nicotinic acid is a specific cure for pellagra and for the somewhat similar nutritional diseases produced by maize diets in dogs and pigs (Chick, Macrae, and Martin) thus appears to be conclusive, and it is now reasonable to ascribe the curative value of liver extracts and yeast, formerly observed in pellagra, to their nicotinic acid content. Ruffin and Smith (1937) found that, whereas crude liver products were effective in relatively small doses in canine blacktongue and in pellagra, larger amounts of more purified extracts were ineffective. These observations, which suggest that a combination of two substances is needed to correct deficiencies in diets which induce blacktongue and pellagra, are difficult to reconcile with the curative effect of such simple substances as nicotinic acid and nicotinamide.

The reaction to nicotinic acid in normal individuals is tingling and increased warmth over the malar regions and neck. Sometimes nausea, vomiting, abdominal cramps and urticaria may ensue. Nicotinic acid and nicotinamide are now dispensed in a convenient form in tablets of 30 to 50 mgm. each. In mild cases 50 mgm. is given three times daily (150 mgm.) for ten to fourteen days, and double that quantity (300 mgm.) in more severe cases. The effect of this treatment upon the pellagrous rash is impressive. Overdosage causes some tingling and numbness of the tongue, and also in the lower jaw along the course of the inferior dental nerve. This treatment should, of course, be backed up by a liberal protein dietary. Riboflavin in maximal doses (3 mgm.) should be added in cases exhibiting signs of ariboflavinosis. The most striking and most easily observable effect of this mode of treatment is seen in the amelioration of the tongue and mouth symptoms. It has a profound effect upon the psychology of the patient as well as on the processes of digestion and assimilation.

The treatment of mental symptoms.—Spies, Aring, Gelperin and Bean submitted 60 cases with mental manifestations to treatment with nicotinic acid, in maximum doses, and *coramine* (the diethylamide of nicotinic acid). These cases showed loss of memory, delirium, mania, or depression ; some had a paranoid reaction. Recovery took place in all within six days. Korsakoff's psychosis and manic depressions were not influenced in the same way. Coramine is injected in doses of 2–5 c.c. daily by the mouth to a total of 20–50 c.c.

Treatment with allied preparations.—Certain of the pyridine carboxylic acids exhibit anti-pellagrous properties. Bills, McDonald and Spies found that pyrazine 2–3 dicarboxylic and pyrazine monocarboxylic acid act like nicotinic acid, curing glossitis and dermatitis. Vilter and Spies claimed that quinolinic acid (2-3–dicarboxylic acid of pyridine) has a therapeutic action on the tongue and mouth symptoms.

Prophylaxis.—In view of the volume and importance of recent researches in this field, it is evident that the prophylaxis of pellagra is bound up in public-health measures and especially in ensuring a well-balanced protein dietary. Whether pellagra can be prevented by the prophylactic administration of nicotinic acid and riboflavin remains to be seen.

CHAPTER XXVI

SCURVY IN THE TROPICS

EPIDEMICS of scurvy are apt to occur among gangs of coolies and labourers who are fed on an unsuitable dietary, especially in natives recruited for labour purposes and fed upon dried cereals and preserved foods, who previously had been in the habit, in their own villages, of subsisting on large quantities of fresh vegetables and fruit such as bananas.

Ætiology.—Scurvy is a food-deficiency disease. It is produced, not by general starvation, but by the absence of an accessory food factor, or vitamin, which can now be prepared synthetically and is known as ascorbic acid. This body (p. 407) is present in all fresh vegetables, including swedes, turnips, and onions, and in fresh fruit, especially the orange and lemon. It is very sensitive to prolonged heat and drying, and therefore is absent from tinned fruits and vegetables, and from dried legumes such as peas and beans, but re-appears directly the latter are induced to germinate. Yeast, fresh meat, and milk contain only small quantities of the antiscorbutic vitamin, and, curious to relate, according to Chick and Hume, preserved *lime* juice little or none at all, while preserved lemon-juice is rich in this substance.

History.—Scurvy was found to be prevented by diet by Kramer (1720); Lind's "Treatise on Scurvy" was published in 1857; infantile scurvy was recognized as a dietetic disease by Barlow (1883). Laboratory experiments by Holst, Frölich, Zilva, Mellanby and others (1907-1929) led to the discovery of vitamin C. The identity of vitamin C and hexuronic acid (ascorbic acid), suggested by Tillmans and Hirsch (1928) was proved by Szent-Györgyi (1928). The constitution was established by Haworth, Hirst and Reichstein (1933), and synthesis effected by Haworth and Reichstein in 1934.

Symptoms.—The onset of scurvy is insidious, with loss of weight, progressive weakness and pallor, and a feeling of stiffness in the leg muscles. The gums soon become affected with a swelling and sponginess of the alveolar margin. As the disease progresses, fungating masses project beyond the teeth, which loosen and fall out. The tongue swells, the salivary and lymphatic glands enlarge, and the breath becomes very foul. The skin becomes dry and rough, and very soon subcutaneous petechiæ form on the limbs and trunk, commencing *around the hair follicles*, especially on the thigh (Fig. 64). Hæmorrhages occur into the muscles of the thigh and into the knee-joint. Very painful

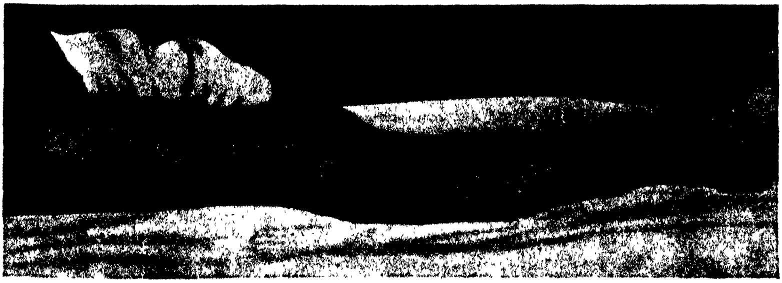


Fig. 64. Scurvy rash in sprue, showing distribution of petechiæ round hair follicles.

effusions under the periosteum form irregular nodes, which may break down and ulcerate. Œdema of the ankles is common, and hæmoptysis or hæmatemesis may occur. Any injury is apt to cause a hæmorrhage.

Together with these objective symptoms the patient experiences cardiac distress, with irregularity of the pulse and hæmic bruits at the apex. The urine is generally loaded with albumin. On the other hand, the digestive system is not disturbed, constipation being more common than diarrhœa. The psychical disturbances are pronounced. Headache is noted early, and delirium supervenes in the later stages. In the most advanced cases the jaw-bones generally become necrotic.

In the young the formation of a "scurvy rosary" at the junction of the costal cartilages, and separation of the epiphyses of the long bones, may occur in a variety known as infantile scurvy, or Barlow's disease.

Scurvy was formerly noted as endemic in the mine-workers on the Rand. Darling and others observed that a certain proportion of these cases was distinct in a clinical sense from those seen elsewhere. In this variety, known as *Rand scurvy,* the spongy gums and loose teeth that occur in the classical type of the disease were absent, while the heart underwent primary hypertrophy, with subsequent dilatation, suggestive of beriberi, though the neuritic symptoms of beriberi were absent, and the knee-jerks exaggerated. Rand scurvy occurred especially among gangs of native labourers when fed upon an unsuitable dietary, particularly natives from the Congo and tropical Africa, who were in the habit of consuming large quantities of fresh vegetables and fruits, and who, when in the mines, were fed on dried cereals and preserved foods. The number of these cases was very large indeed. Donaldson reported that in 1920 more than 200 cases of scurvy were treated in one hospital, of which one-third occurred within three months of entering the mines. It was found that scurvy in these natives predisposed to all kinds of bacterial infections, and especially to pneumonia. Where the diet was deficient but not entirely lacking in vitamin C, actual symptoms of scurvy did not manifest themselves, but such individuals were very liable to bacterial infections owing to degenerative changes in the bone-marrow.

Diagnosis.—To diagnose scurvy under modern conditions is no difficult matter; but care must be taken to distinguish mild cases from pyorrhœa alveolaris. A method of diagnosis in the early stages, especially in children, was devised by Hess. The arm-band of a sphygmomanometer is placed upon the arm and inflated until the pressure reaches 90 mm., and the venous circulation is shut off. This pressure should be maintained for three minutes and then released. As soon as the cyanosis fades, an examination should be made for the petechial spots which may confirm the diagnosis of scurvy. This test depends on increased fragility of the capillary endothelium. Rotter introduced an *intradermal test* with dichlorphenol-indophenol. (For the technique of this test, as well as of the demonstration of vitamin C in the urine, *see* p. 410.)

Differential diagnosis has to be made from blood diseases such as leukæmia, and essential thrombocytopenia (onyalai, *see* p. 673).

Treatment.—This is chiefly dietetic. The disease, if recognized early, readily yields to a diet composed of fresh fruit and vegetables; when these are unprocurable, fresh meat can be substituted, but is by no means so satisfactory.

Raw onions are very valuable antiscorbutics, and raw potatoes and swedes have a definite curative value. Canned vegetables, except canned tomatoes, are useless.

For natives, the most valuable antiscorbutic foods are orange, lemon, and pawpaw juice, sweet potatoes, and green mealies. Incompletely fermented beer, such as the Kaffir beer, made from germinating grain, is said to be of considerable value, but this is doubtful.

Vaughan, Hunter and others reported brilliant successes in the treatment of scurvy with synthetic ascorbic acid. Many cases were reported by Schultzer, Parsons, Harris, Ray, and Szent-Györgyi; 40–100 mgm. of ascorbic acid are given intravenously to an adult for ten days with success; to infants 30–60 mgm. daily by the mouth for about fourteen days.

Germinating peas are useful when fresh vegetables are unobtainable. The following method of using peas and other pulses is recommended by Chick and Hume:

SUGGESTED METHODS OF PREPARING PEAS, LENTILS, OR OTHER PULSES FOR THE PREVENTION OF SCURVY, IN THE ABSENCE OF FRESH VEGETABLES

1. The dry seeds must be whole, retaining the original seed-coat, and not milled or decorticated.

2. They must be soaked in water for several hours; the time necessary depends on the temperature—24 hours at 50° to 60° F., and 12 hours or less at 90° F.

3. The water must then be drained away, and the peas allowed to remain moist with access of air. They will then germinate and the small rootlet grow out. This germination will take 48 hours at 50° to 60° F., and 12 to 24 hours at 80° F.

Soaking.—The peas or other pulses, placed in a *clean* sack, should be steeped in a trough, barrel, or other suitable vessel, full of clean water, and should be occasionally stirred. The sack and trough should be large enough to allow for the swelling of the peas to about three times their original size. In a hot climate 6 to 12 hours should suffice for this soaking.

Germination.—The peas should be lifted out of the water and spread out to a *depth not exceeding 2 to 3 inches* in a trough or other vessel with sides and bottom porous or well perforated with holes; this is to allow *complete* access of air. *The seeds must be kept in a moist atmosphere*, by covering with damp cloth or sacking, which is sprinkled (by hand or automatically) as often as is required to keep the peas thoroughly moist underneath. *All the vessels should be clean.*

4. *It is important that the germinated pulses should be cooked and eaten as soon as possible after germination, and should not be allowed to become dry again*; in that case the antiscorbutic properties acquired during the process of germination will again be destroyed. The pulses should not be cooked longer than necessary.

Prophylaxis.—The prevention of scurvy consists in providing a diet adequate in vitamin C. It should be the duty of health authorities and medical officers of industrial undertakings to insist that native labourers are adequately fed. The old and evil idea that African natives can subsist on maize meal, salt and dried beans should be most vigorously suppressed. It has been pointed out that one factor in the production of scurvy in native African races is the prolonged overcooking[1] and steaming of food, especially of vegetables. It is, therefore, important that in gangs of unmarried natives efficient cooks should be appointed. As a general rule, the food cooked by native women is much more hygienic and palatable than that prepared by men.

Wherever possible, in mines or tropical camps, native gardens should be established. Men threatened with scurvy should be given light work only.

---

[1] When cabbage is cooked for one hour at temperatures ranging from 80–100° C. the leaves lose 90 per cent. of their antiscorbutic value.

Ætiology. *Discovery of the comma bacillus, or vibrio.*—The cholera vibrio was first discovered by Koch in Egypt in 1883; this discovery he confirmed in Calcutta in 1884 by finding it in every case of the disease examined. His observations have since been abundantly confirmed.

Description of the cholera vibrio.—The comma bacillus (Fig. 65) is a very minute organism, 1·5 to 2 μ in length by 0·5 to 0·6 μ in diameter—about half the length and twice the thickness of the tubercle bacillus. It is generally slightly curved like a comma; hence its name. After appropriate staining, flagella can be distinguished at each end or at one end only—sometimes one, sometimes (though less frequently) two. These flagella, though of considerable length—from one to five times that of the body of the bacillus—are difficult to see in ordinary preparations owing to their extreme tenuity. They are not always present during the entire life of the parasite. They impart very active spirillum-like movements. The individual bacilli, when stained, show darker parts at the ends or at the centre. Sometimes in cultures two or more bacilli are united, in which case an S-shaped body is the result; or several bacilli may be thus united, producing a spirillar appearance.

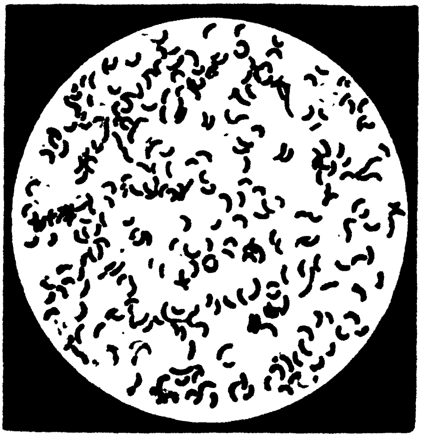


Fig. 65.—Cholera vibrio. Agar culture: 24 hours' growth. × 1,000. (*Muir and Ritchie.*)

The comma bacillus is easily stained by watery solutions of fuchsin, or by Löffler's method, dried cover-glass films being used. It is decolorized by Gram.

The bacillus grows best in alkaline media at a temperature of from 30° to 40° C. Growth is arrested below 15° or above 42° C.; a temperature over 50° C. kills the vibrio. Meat broth, blood-serum, nutrient gelatin, and potato are all suitable culture media. It multiplies rapidly without curdling in milk; it dies rapidly in distilled water; it survives longer if salt be added to the water—for instance, 285 days in sea-water.

In gelatin plates it grows readily as minute white colonies, irregular in shape, and granular, with surrounding liquefaction, into which the colonies of vibrios sink as into funnel-shaped depressions. In gelatin stab-cultures the growth at first is most active near the surface; later, as growth proceeds along the needle track, a finger-shaped liquefaction results, which in time extends to the sides of the tube. In older cultures involution forms are common; they may die out after five or six weeks.

Agar is not liquefied, and in it cultures retain their vitality longer. On potato, at 20° to 30° C., the culture appears as a thin, brownish, porcelain-like film. In broth some of the bacilli form a scum on the surface; others, falling in masses to the bottom, leave the body of the liquid clear. As a rule, the cholera vibrio does not produce hæmolysis, if blood be added to the medium such as agar, after twenty-four hours' incubation. The test is best performed in a fluid medium by adding varying amounts, from 1 c.c. downwards, of a three days' culture in alkaline broth to 1 c.c. of a 5 per cent. suspension of goat's corpuscles, and then thoroughly mixing. After incubation for two hours the tubes are placed in the ice-chest overnight and read the next day. With the solutions of sugars (1 per cent.) usually employed, the vibrio produces acid, without gas-formation, in glucose, mannite, saccharose, and maltose. Fermentation of lactose, with acid production, occurs two or three days later. The cholera-red reaction is obtained by the addition of pure sulphuric acid to a culture in 1 per cent. peptone solution.

The true cholera vibrio belongs to Heiberg's Type I, and ferments mannose and saccharose, but not arabinose. It gives positive cholera red and negative Voges-Proskauer reactions; but does not produce early hæmolysis of erythrocytes. These characters alone, however, are not enough for more than presumptive identification, since some non-pathogenic vibrios have most of them. The true cholera vibrio is agglutinated by serum prepared against the O variants of Ogawa and Inaba strains, and this is the principal means of differentiation (Gardner and Venkatraman).

Until recently a considerable amount of hesitation was felt by many authorities in accepting the cholera vibrio as the true germ-cause of cholera.

Certain organisms, known as the paracholera, or inagglutinable vibrios (Finkler-Prior and El-Tor), resemble the cholera vibrio minutely. Organisms found in fowl cholera, in decomposed cheese, and in river water also resemble it very closely but, as they behave somewhat differently in the serological sense, they must be considered biologically distinct. Cultures of cholera vibrios have been swallowed many times by way of experiment, and, although in some instances diarrhœa has resulted, in only one case has true cholera been produced. Probably for the production of cholera several conditions are necessary, of which the comma bacillus is only one. The difficulty of producing true cholera in lower animals by the administration of cholera cultures has exercised the minds of many, especially in the days following Koch's discovery, but more recently cholera-like symptoms have been produced in ground-squirrels by administering cultures of the organisms in alkaline media.

The exact significance of the non-agglutinating vibrios still remains a matter of debate. Doorenbos brought forward evidence that the El-Tor vibrio and other vibrios which behave somewhat differently are, in fact, the true cholera vibrio contaminated with bacteriophage. Formerly the association of epidemic cholera with a hæmolytic El-Tor vibrio was not considered possible, but de Moor and others in 1938 found that the epidemic in Celebes was caused by a typical El-Tor vibrio as shown by its cultural and serological characters. This vibrio belongs to Gardner and Venkatraman's subgroup O, Heiberg's type I, and is hæmolytic to goat cells. The epidemic caused by it came to an end in six months and did not occur again. This vibrio gave positive Voges-Proskauer and cholera red reactions and the agglutinability was not affected by heat as in the true cholera vibrio. Taylor regarded this form as practically non-existent in India in man, but as representative of certain water vibrios in Bengal. The general conclusion is that the two vibrios, though identical in antigenic structure, do represent different species and that the El-Tor vibrio occupies an intermediate position

Section III.—ABDOMINAL DISEASES

CHAPTER XXVII

CHOLERA

Synonym. Cholera Asiatica.

Definition.—Cholera (Χοληροια = flow of bile) is an acute, infectious, epidemic disease, characterized by profuse purging and vomiting of a colourless watery material, by muscular cramps, suppression of urine, algidity and collapse, the presence of the cholera vibrio in the intestines, and by a high mortality.

History and geographical distribution.—It is probable that from remotest antiquity cholera has been endemic in Lower Bengal and in Central China, and has from time to time spread as an epidemic over India. In 1817 it began to extend all over Asia, eastwards as far as Peking and Japan, southwards to Mauritius, and westwards to Syria and the eastern shores of the Caspian. Stopping short at Astrakhan in 1825, it did not on that occasion invade Europe. Since 1830, when cholera first visited Europe, there have been at least five epidemics—1848–51, 1851–55, 1865–74, 1884–86, and 1892–95. Minor epidemics have occurred in Europe since, but have been restricted. During the Balkan War of 1913, and in the course of the 1914–18 war, especially in the Balkans and in Iraq, there were many outbreaks of cholera, but the disease did not extend as an epidemic beyond the actual seat of war.

The 1870–73 epidemic practically spared Great Britain, but it crossed the Atlantic and, entering by way of Jamaica and New Orleans, raged for a time in the United States.

From a study of the march of these epidemics it is to be concluded that cholera reaches Europe by three distinct routes—(1) *via* Afghanistan, Persia, the Caspian Sea, and the Volga valley; (2) *via* the Persian Gulf, Syria, Asia Minor, Turkey in Europe, and the Mediterranean; (3) *via* the Red Sea, Egypt, and the Mediterranean.

Epidemiology and endemiology.—Cholera follows the great routes of human intercourse, and is conveyed chiefly by man—probably in its principal extensions by man alone—from place to place. In India, during religious gatherings, hundreds of thousands of human beings are collected together under highly insanitary conditions, as at the Hurdwar and Mecca pilgrimages. Cholera breaks out among the devotees, who, when they separate, carry the disease along with them as they proceed towards their homes, infecting the people of places they pass through. The Hedjaz has, for the last 100 years, been the point of relay of cholera in its progress from the Far East towards the West. During that period there have been more than 27 outbreaks. In India cholera appears to spread from its home in Lower Bengal over the northern and western, central, and southern provinces in a series of waves of two to four years' duration. Cholera never travels faster than a man can travel; but in modern times, owing to the increased speed of locomotion and the increased amount of travel, epidemics advance more rapidly and pursue a more erratic course than they did eighty years ago. On the other hand, isolated countries, such as the Andaman

Islands, Australia, New Zealand, the Pacific islands, the Cape Province, and the West Coast of Africa, have so far escaped. An epidemic of considerable virulence occurred in Celebes (Dutch East Indies) in 1938 and exhibited several peculiar features.

Truly endemic cholera centres are found in Lower Bengal and in the Yangtse Valley, China. According to Taylor, the recognition of an endemic area is :—

(*a*) one in which the total number of months with absence of cholera deaths does not exceed 30 in 32 years ;

(*b*) one in which a break of five or more months in cholera incidence does not take place.

There are two types of outbreak of cholera, according to whether the general water-supply is contaminated or contamination is localized to certain wells, cisterns, etc. In the former instance the outbreak is explosive and cases occur simultaneously in all parts of the city and disappear again with almost equal suddenness. In the Hamburg epidemic of 1892, during a period of only two months, cholera attacked 17,000 persons, causing 8,605 deaths in a population of 600,000. The water-supply of Hamburg was taken directly from the river, while the adjoining city, Altona (population 140,000) filtered its water from the river by a slow sand process. Although Altona lies further down the river and is contaminated with the sewage of Hamburg, yet the deaths in Altona were only 2·1 per mille as against 13·4 per mille for Hamburg. To illustrate the second type of transmission, there is the well-known incident of the Broad Street pump in 1854. This was the first definite proof of the association of cholera with water. It was noted that cholera was ten times more prevalent in Golden Square than in other parts of London, and increased in the neighbourhood of the Broad Street well. The employees of a factory where the well water was used had a large number of cases, while an adjoining brewery which had a well of its own did not furnish a single case.

Rogers believed that the condition necessary for the spread of cholera in India is an absolute humidity of over 0·400, and that by watching the climatic conditions which influence the seasonal and annual incidence of cholera, increased or epidemic prevalence should usually be foreseen in time for steps to be taken to lessen its spread.

The forecasting of cholera epidemics has therefore become an actual possibility. Based upon statistics which have been subjected to modern scientific analysis, an outbreak can be predicted two to three months ahead. All the co-efficients of correlation between the measure of cholera incidence and other variables to the highest order have been taken into consideration. The association of high relative humidity with high temperature, accompanied by intermittent rains, forms the most favourable atmosphere for the development of the disease, and the presence of endemic centres, from which epidemics may at any time spring, must also be accepted. Indian observers have recently found, on analysis according to the periodogram method, that in South India cholera occurs in a periodicity of six years.

D'Herelle made the interesting suggestion that the rise and fall of epidemics of cholera may be due to the amount of bacteriophage produced. Patients in whose stools no bacteriophage appears die of cholera. Those cases in whom bacteriophage is strong from the outset, rapidly recover.

Ætiology. *Discovery of the comma bacillus, or vibrio.*—The cholera vibrio was first discovered by Koch in Egypt in 1883; this discovery he confirmed in Calcutta in 1884 by finding it in every case of the disease examined. His observations have since been abundantly confirmed.

Description of the cholera vibrio.—The comma bacillus (Fig. 65) is a very minute organism, 1·5 to 2 μ in length by 0·5 to 0·6 μ in diameter—about half the length and twice the thickness of the tubercle bacillus. It is generally slightly curved like a comma; hence its name. After appropriate staining, flagella can be distinguished at each end or at one end only—sometimes one, sometimes (though less frequently) two. These flagella, though of considerable length—from one to five times that of the body of the bacillus—are difficult to see in ordinary preparations owing to their extreme tenuity. They are not always present during the entire life of the parasite. They impart very active spirillum-like movements. The individual bacilli, when stained, show darker parts at the ends or at the centre. Sometimes in cultures two or more bacilli are united, in which case an S-shaped body is the result; or several bacilli may be thus united, producing a spirillar appearance.

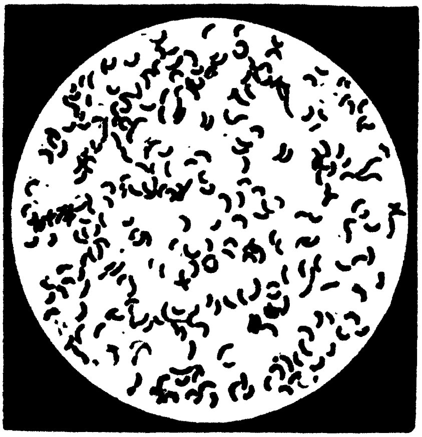


Fig. 65.—Cholera vibrio. Agar culture: 24 hours' growth. × 1,000. (*Muir and Ritchie.*)

The comma bacillus is easily stained by watery solutions of fuchsin, or by Löffler's method, dried cover-glass films being used. It is decolorized by Gram.

The bacillus grows best in alkaline media at a temperature of from 30° to 40° C. Growth is arrested below 15° or above 42° C.; a temperature over 50° C. kills the vibrio. Meat broth, blood-serum, nutrient gelatin, and potato are all suitable culture media. It multiplies rapidly without curdling in milk; it dies rapidly in distilled water; it survives longer if salt be added to the water—for instance, 285 days in sea-water.

In gelatin plates it grows readily as minute white colonies, irregular in shape, and granular, with surrounding liquefaction, into which the colonies of vibrios sink as into funnel-shaped depressions. In gelatin stab-cultures the growth at first is most active near the surface; later, as growth proceeds along the needle track, a finger-shaped liquefaction results, which in time extends to the sides of the tube. In older cultures involution forms are common; they may die out after five or six weeks.

Agar is not liquefied, and in it cultures retain their vitality longer. On potato, at 20° to 30° C., the culture appears as a thin, brownish, porcelain-like film. In broth some of the bacilli form a scum on the surface; others, falling in masses to the bottom, leave the body of the liquid clear. As a rule, the cholera vibrio does not produce hæmolysis, if blood be added to the medium such as agar, after twenty-four hours' incubation. The test is best performed in a fluid medium by adding varying amounts, from 1 c.c. downwards, of a three days' culture in alkaline broth to 1 c.c. of a 5 per cent. suspension of goat's corpuscles, and then thoroughly mixing. After incubation for two hours the tubes are placed in the ice-chest overnight and read the next day. With the solutions of sugars (1 per cent.) usually employed, the vibrio produces acid, without gas-formation, in glucose, mannite, saccharose, and maltose. Fermentation of lactose, with acid production, occurs two or three days later. The cholera-red reaction is obtained by the addition of pure sulphuric acid to a culture in 1 per cent. peptone solution.

The true cholera vibrio belongs to Heiberg's Type I, and ferments mannose and saccharose, but not arabinose. It gives positive cholera red and negative Voges-Proskauer reactions; but does not produce early hæmolysis of erythrocytes. These characters alone, however, are not enough for more than presumptive identification, since some non-pathogenic vibrios have most of them. The true cholera vibrio is agglutinated by serum prepared against the O variants of Ogawa and Inaba strains, and this is the principal means of differentiation (Gardner and Venkatraman).

Until recently a considerable amount of hesitation was felt by many authorities in accepting the cholera vibrio as the true germ-cause of cholera.

Certain organisms, known as the paracholera, or inagglutinable vibrios (Finkler-Prior and El-Tor), resemble the cholera vibrio minutely. Organisms found in fowl cholera, in decomposed cheese, and in river water also resemble it very closely but, as they behave somewhat differently in the serological sense, they must be considered biologically distinct. Cultures of cholera vibrios have been swallowed many times by way of experiment, and, although in some instances diarrhœa has resulted, in only one case has true cholera been produced. Probably for the production of cholera several conditions are necessary, of which the comma bacillus is only one. The difficulty of producing true cholera in lower animals by the administration of cholera cultures has exercised the minds of many, especially in the days following Koch's discovery, but more recently cholera-like symptoms have been produced in ground-squirrels by administering cultures of the organisms in alkaline media.

The exact significance of the non-agglutinating vibrios still remains a matter of debate. Doorenbos brought forward evidence that the El-Tor vibrio and other vibrios which behave somewhat differently are, in fact, the true cholera vibrio contaminated with bacteriophage. Formerly the association of epidemic cholera with a hæmolytic El-Tor vibrio was not considered possible, but de Moor and others in 1938 found that the epidemic in Celebes was caused by a typical El-Tor vibrio as shown by its cultural and serological characters. This vibrio belongs to Gardner and Venkatraman's subgroup O, Heiberg's type I, and is hæmolytic to goat cells. The epidemic caused by it came to an end in six months and did not occur again. This vibrio gave positive Voges-Proskauer and cholera red reactions and the agglutinability was not affected by heat as in the true cholera vibrio. Taylor regarded this form as practically non-existent in India in man, but as representative of certain water vibrios in Bengal. The general conclusion is that the two vibrios, though identical in antigenic structure, do represent different species and that the El-Tor vibrio occupies an intermediate position

between the cholera and non-agglutinable vibrios. The virulence of the cholera vibrio can be exalted by passage through guinea-pigs and successive culturing of the peritoneal exudate of intraperitoneally injected animals alternating with culture media growth inoculations. Such a fixed virus, the virulence of which cannot be exalted, formed the material used by Haffkine for cholera vaccine.

Gardner and Venkatraman (1935) made a thorough examination of the whole cholera-group question. They found that heat-stable antigens are divisible into: (*a*) a considerable number of specific antigens which are best demonstrated by O group sera and H-O suspensions, which serve as a basis of classification into O subgroups, and (*b*) a non-specific component which is demonstrable with O sera and O suspensions.

Taylor conducted an investigation on the serology of vibrios in which a standard O antigen was used. This is prepared in a dry form and testing sera were prepared from this dried antigen. Two main subtypes of *V. choleræ* were used which contained the common O and in addition its own specific antigen. The result indicated that vibrios isolated from true cholera cases, but which do not conform to the serological O group I, are mere accompaniments of the true cholera vibrio and are intestinal inhabitants as much of the non-cholera as of the cholera-stricken population.

Toxins.—Filtered cultures of the cholera vibrio have little toxic action, the virus being apparently liberated by disintegration of individual organisms. Dead cultures, given by the mouth, produce no effect, unless the intestinal epithelium is injured. The toxins are mostly destroyed at 60° C.; when ground up and frozen by liquid air, an extract of high toxicity to laboratory animals, especially when injected intravenously, is obtained. The organism multiplies in the small intestine, and liberates an endotoxin which is responsible for desquamation of the epithelium and other manifestations of the disease.

Phan was able to produce the clinical phenomena of cholera in guinea-pigs by injecting cholera endotoxin in doses of 0·05–0·1 c.c. in the neighbourhood of the splanchnic nerves. Similar results were obtained in rabbits by injecting doses of 0·2 c.c.

Methods of infection.—Infected material is conveyed from sick to healthy persons, either by water, food, or infected linen. Milk, raw fruit, vegetables and other uncooked foods are all able to serve as media for the transference of the vibrio. Clothing, if kept moist, can retain the infectivity for days and weeks. Greig has shown in India that, in stools kept in the dark at room temperatures, the average life of the vibrio is about eight days, but when dried it only survives for a few hours. In water the vibrios remain viable for a considerable time. In reservoir water they live about two weeks, but some grossly contaminated streams, such as the Ganges, are unfavourable to their survival.

Cholera carriers.—Patients who have recovered from cholera may continue to excrete the vibrio irregularly for a few weeks, but, as a rule, 90 per cent. become free from infection in 14 days and 99 per cent. in a month. The existence of apparently healthy cholera carriers has been recognized, and these may excrete vibrios for two months, though the "carrier," such as is known in typhoid, does not exist for cholera. Taylor definitely states that the convalescent and contact carriers in most cases are free from the vibrio five days from the onset of the attack or contact.

Immunity.—The guinea-pig or rabbit may easily be immunized against the cholera vibrio by repeated intraperitoneal injections of killed cultures. The serum thus obtained shows marked agglutinative properties in a high titre to cultures of the organism. Furthermore, this serum, when injected into a non-immune animal, has marked protective power against even four or five times the lethal dose. When this happens, active bacteriolysis takes place (Pfeiffer's reaction). The test is performed as follows :

A loopful of a young agar-culture of the vibrio is added to 1 c.c. of bouillon containing 0·001 c.c. of anti-cholera serum, and is injected into the peritoneal cavity of a young guinea-pig ; by means of capillary tubes inserted into the peritoneum, the peritoneal fluid is examined microscopically every few minutes. If the original culture was a true cholera vibrio, the organisms break up into globules ; if not, no change takes place. The inoculation of animals by cholera cultures produces an immune serum which is remarkable for its high agglutinating power, the titre going as high as 1 in 12,000. For an agglutination test to prove that vibrios isolated from the stools are those of true cholera, a serum of a titre of 1 in 4000 should be used.

Pathology.—Rigor mortis occurs early and persists for a considerable time. Curious movements of the limbs may take place in consequence of post-mortem muscular contractions. On dissection, the most characteristic pathological appearances in cholera are those connected with the circulation and with the intestinal tract.

If death occurred during the algid stage, the surface presents a shrunken and livid appearance. All the tissues are abnormally dry. The muscles are dark and firm ; sometimes one or more of them are ruptured—evidently from the violence of the cramps during life. The right side of the heart and the systemic veins are full of dark, thick, and imperfectly coagulated blood which tends to cling to the inner surface of the vessels. Fibrinous clots, extending into the vessels, may be found in the right heart. The lungs are usually anæmic, dry, and shrunken, occasionally congested and œdematous. The pulmonary arteries are distended with blood, the veins empty. The liver is generally loaded with blood ; the gall-bladder full of bile ; the spleen small. Like all the other serous cavities, the peritoneum contains no fluid, its surface being dry and sticky. The outer surface of the bowel has generally a diffuse rosy-red, occasionally an injected appearance. It contains a larger or smaller amount of the characteristic rice-water material, occasionally blood. The mucous membrane of the stomach and intestine is generally pinkish from congestion, or there may be irregular arborescent patches of injection here and there throughout its extent.

If death occurred during the stage of reaction, the tissues are moist ; the venous system is less congested ; the lungs are probably congested and œdematous, perhaps inflamed. Very probably there are evidences of extensive enteritis.

Greig has shown that the gall-bladder and biliary passages are frequently invaded by the cholera vibrio and that, as in enteric, this viscus may act as a reservoir of infection. Occasionally, according to the same authority, cholera may be a septicæmia ; the vibrios have sometimes been demonstrated in the substance of the lungs and kidneys, and in the spleen.

On microscopical examination of the contents of the bowel during the acute stage of the disease the cholera vibrio, in most cases, may be demonstrated. Usually it is in great abundance, occasionally in almost pure culture in the upper part of the small intestine and duodenum, but it may be very scarce in the large gut. Sections of the intestine show the vibrio lying on and between the epithelial cells of villi and glands.

Bannerjee and Dutta demonstrated focal necrosis in the kidneys with hyaline changes and sclerotic atrophy. There are also marked changes in the convoluted tubules.

Symptoms.—Although cholera may declare itself within a few hours of exposure to infection, it may also do so at any time up to ten days. Three to six days may be set down as the usual incubation period. An attack of cholera commences in one of two ways: either it may supervene in the course of what appears to be an ordinary case of diarrhœa, or it may come on suddenly, without any well-marked prodromal stage. During cholera epidemics diarrhœa is unusually prevalent. It is a common observation that at such times an attack of simple diarrhœa may, after a day or two, assume the characters of true cholera. The preliminary looseness in such cases is known as premonitory diarrhœa or cholerine and is, in fact, a mild form of cholera. Besides diarrhœa, other prodromata, such as languor, depression of spirits and noises in the ears are sometimes noted.

Description of the average case.—When true cholera sets in, profuse watery stools, usually associated with griping pains, and at first fæcal in character, pour, one after the other, from the patient. Quickly the stools lose their fæcal character, becoming colourless or, rather, like thin rice-water containing small white flocculi in suspension. Enormous quantities—pints—of this material are generally passed. Presently, vomiting, also profuse, at first perhaps of food, but very soon of the same rice-water material, supervenes. Agonizing cramps attack the extremities and abdomen; the implicated muscles stand out like rigid bars, or are thrown into lumps from the violence of the contractions. The patient may rapidly pass into a state of collapse. In consequence principally of the loss of fluid by the diarrhœa and vomiting, the soft parts shrink, the cheeks fall in, the nose becomes pinched and thin, the eyes sunken, and the skin of the fingers shrivelled like a washerwoman's. The surface of the body becomes cold, livid, and bedewed with a clammy sweat; the urine and bile are suppressed; respiration is rapid and shallow; the breath is cold, and the voice is sunk to a whisper. The pulse soon becomes thready, weak, and rapid, and then after coming and going and feebly fluttering, may disappear entirely. The surface temperature sinks several degrees below normal—to 93° or 94° F.; whilst that in the rectum may be several degrees above normal—101° to 105° F. The blood pressure is low. The systolic may register 50 mm. of mercury but is frequently unregistrable. The patient is now restless, tossing about uneasily, throwing his arms from side to side, feebly complaining of intense thirst and of a burning feeling in the chest, and racked with cramps. Although apathetic, the mind generally remains clear. In other instances the patient may wander or may pass into a comatose state.

This, the "algid stage" of cholera, may terminate in one of three ways—in death, in rapid convalescence, or in febrile reaction.

When death from collapse supervenes, it may do so at any time from two to thirty hours from the commencement of the seizure, usually in from ten to twelve. On the other hand, the gradual cessation of vomiting and purging, the re-appearance of the pulse at the wrist, the increase of blood pressure and the return of some warmth to the surface may herald convalescence. In such a case, after many hours' absence, secretion of urine returns, and in a few days the patient may be practically well again.

Usually, however, a condition known as the " stage of reaction " gradually supervenes on the algid stage.

Anuria.—The first signs of anuria are congestion of the mucous membranes and conjunctivæ, malar flush, delirium, and gradual increase in depth and rate of respiration. Recovery is marked by the passage of a few ounces of turbid, highly coloured urine and this is followed by a " critical diuresis " resembling that seen in some cases of acute glomerulonephritis.

Renal failure in cholera has been compared to anuria following crush injuries. Tomb claimed that it may be explained by the hypothesis of Freeman that collapse of the circulation, as in surgical and traumatic shock, is the result of over-stimulation of the sympathetic nervous system. This results in dilatation of the capillaries of the skeletal muscles and constriction of the dermal and abdominal vessels. It is suggested that the histological changes in the urinary tubules are due to deprivation of oxygen. The blood area is invariably raised and may reach 350 mgm. Anuria may persist for fifty hours, and the patient may yet recover.

The importance of charting the amount of urine, hour by hour, day by day, in the reactionary stage of cholera cannot be over-emphasized. These data are essential if threatened anuria is to be successfully combatted.

Reaction or cholera typhoid.—When the patient enters on this stage the surface of the body becomes warmer, the pulse returns, the face fills out, restlessness disappears, urine is secreted, and the motions diminish in number and amount, becoming bilious at the same time. Coincidently with the subsidence of the more urgent symptoms of the algid stage and this general improvement in the appearance of the patient, a febrile condition of greater or less severity may develop. Minor degrees in this reaction generally subside in a few hours ; but in more severe cases the febrile state becomes aggravated, and a condition in many respects closely resembling typhoid fever, " cholera typhoid," ensues.

During the stage of reaction death may occur from a variety of complications—from pneumonia, from enteritis and diarrhœa, from asthenia, or from such effects of uræmic poisoning as coma and convulsions.

Hyperpyrexia is an occasional, though rare, occurrence in cholera. In such cases the axillary temperature may rise to 107° F., the rectal temperature perhaps to 109° F. These cases also are almost invariably fatal.

In cholera there is a considerable variety in the character of the symptoms and in their severity, both in individual cases and in different epidemics. It is generally stated that the earlier cases are the more severe, those occurring towards the end of the epidemic being on the whole milder.

Ambulatory cases occur during all epidemics, characterized by diarrhœa and malaise merely ; there is never complete suppression of urine, the diarrhœa never loses its bilious character, and is not accompanied by cramps. The attack gradually subsides without developing a subsequent stage of reaction.

Cholera sicca.—A very fatal type is known as " cholera sicca." In these cases, though there is no, or very little, diarrhœa or vomiting, collapse sets in so rapidly that the patient is quickly overpowered as by an overwhelming dose of some poison, and dies in a few hours without purging or any attempt at reaction.

Eye changes in cholera.—Osmotic dehydration in cholera can bring about a lens opacity, which, in lesser degrees, is reversible, so far as the physical state of the water in the lens is involved.

Therefore cataract may develop suddenly in the stage of collapse and may have a similar osmotic basis to that of diabetes. In cholera loss of fluid from the bowel may lead to osmotic dilution of the body fluids, including the aqueous, and consequent inflow of water into the lens.

The ophthalmoscopic changes consist of a wavy gridiron appearance with dark lines against a red background, possibly denoting wrinkling of the capsule.

These changes disappear on rehydration.

Sequelæ are unusual. Recovery is generally complete. Occasionally there are minor sequelæ, such as anæmia, mental and physical debility, insomnia, a diphtheritic inflammation of the mucous membranes of the intestines, fauces and genitalia, nephritis, different forms of pulmonary inflammation, parotitis apt to end in abscess, ulceration of the corneæ, boils, bedsores, and gangrene of different parts of the body. Jaundice occurs at times, and is said to be of the gravest import. An interesting, but unusual, sequel is bradycardia. Pregnant women almost invariably miscarry, the fœtus showing evidences of cholera.

The prognosis of cholera is especially bad in opium addicts.

Mortality.—The average case-mortality in cholera amounts to about 50 per cent. Some epidemics are more deadly than others. As already mentioned, the mortality is greater in the earlier than in the later stages of an epidemic. To the old, the very young, the pregnant, the subjects of grave organic disease—particularly of the liver, kidneys, and heart—the dissipated, the underfed, and the feeble, the danger is very great.

Diagnosis.—During the height of an epidemic the diagnosis of cholera is generally easy ; the profuse rice-water discharges, the collapse, the cold clammy skin, the cyanosis, the shrunken features, shrivelled fingers and toes, the feeble husky voice, the cold breath, the cramps, and the suppression of urine, together with the high rate of mortality, are generally sufficiently distinctive. But in the first cases of some outbreaks of diarrhœa, which may or may not turn out to be cholera, and the true nature of which, for obvious reasons, it is important to determine, correct diagnosis may not be so easy. Control measures should be applied if the clinical evidence is suggestive, without waiting for bacteriological confirmation.

In other forms of diarrhœa it is rare for the stools to be persistently so entirely devoid of biliary colouring matter as they are in cholera.

The detection of the comma vibrio in the stools is regarded as a positive indication of cholera. It would be rash, however, to affirm that a negative result from bacteriological examination of a single case rules out cholera. Moreover, such examinations, to be trustworthy, have to be made by a skilled bacteriologist.

In the first place the stools should be examined microscopically. If vibrios are present in large numbers they may be detected by their scintillating rotatory movements in hanging-drop preparations, or by their characteristic shape in fæcal films stained by carbolfuchsin. According to Koch, a rough diagnosis may be made in 50 per cent. of cases by this method. If vibrios are very numerous, plates may be spread direct by a platinum loop on alkaline agar, or on Dieudonné's medium. When the vibrios are present in small numbers—(*a*) alkaline peptone water should be inoculated with two or three loopfuls of the fluid stool and incubated for seven hours; (*b*) any pellicle present on the surface of the broth should be examined in stained films or by the hanging-drop method; (*c*) if vibrios are scanty, a second alkaline peptone tube should be reinforced by inoculation, incubating for a further six to eight hours, and plating out on alkaline agar; (*d*) an emulsion of colonies from the plate or from an agar slope sub-culture should be agglutinated against the specific antiserum in high titre.

An agglutination of over 1 in 1000 with a specially prepared serum strongly suggests the true cholera vibrio, which may then be subjected to special biochemical tests.

The full technique of identification demands a considerable amount of time, and as promptness is the first essential in cholera diagnosis, be it of acute cases or of "carriers," other methods of rapid and more or less accurate diagnosis have been devised. Such a one is Bandi's method, which consists in inoculating the suspected fæces into peptone water containing agglutinating serum of such strength as to clump the cholera bacillus in high dilution. Within as short a period as three hours' incubation, agglutination visible to the naked eye is said to be present. This method, when employed in a large number of cases, necessarily consumes a large quantity of immune serum.

The advantages of such a rapid method are several: positive reports may be obtained on a large number of cases in as short a period as eighteen hours, and as many as 200 stools may be examined by one worker during the course of a morning's work. A modification was described by Davies and the Editor. The following are the stages in the technique:

1. Inoculate a platinum loopful of fæces into peptone water, 1 per cent. peptone, 1 per cent. NaCl, made distinctly alkaline to litmus.
2. Incubate for eighteen hours.
3. Place a drop of the resulting growth on the slab of Garrow's agglutinometer (Appendix, p. 1014), together with a drop of 1 in 80 anti-cholera serum. The resulting mixture will give a dilution of cholera serum 1 in 160. On the next partition drop an equal quantity of normal saline, together with a drop of the peptone culture, to act as a control. Rotate for three minutes. If vibrios are present, a definite agglutination will be obtained. This can be confirmed later by agglutinating with cholera serum in still higher dilutions. It is recommended that stock bottles (with rubber caps) of cholera serum preserved with 0·5 per cent. carbolic acid, in dilutions 1 in 80, 1 in 160, 1 in 320, 1 in 640, be kept. If an agglutination is obtained with the lower dilutions it may subsequently be titrated with the higher ones.
4. The peptone culture can then be spread with a platinum loop on Crendiropoulo's agar (alkaline agar), and a culture obtained by this means. The cholera colonies can then easily be recognized by their transparent bluish-grey appearance. The hæmolytic and sugar tests may then be applied. It has been found that vibrios agglutinating with specific serum in high dilutions invariably give correct sugar, hæmolytic, and cholera-red reactions (p. 451).

In an autopsy on a suspected case of cholera, at least two sections of the small gut, each about 5 in. in length—one just above the ileocæcal valve, the other in the middle of the ileum—should be ligatured, cut off, dropped into sterile saline and sent to a bacteriological laboratory as soon as possible for examination.

An agglutination reaction is not obtainable from the blood-serum during the acute stage, but it is present after eight to ten days from the commencement of the disease, reaching its maximum in four weeks ; it may attain a titre of 1 in 1000.

Taylor made it plain that the question of H and O agglutinins is important in the diagnosis of cholera, as it is in other intestinal diseases of bacterial origin. The H element is present in some strains of true cholera and also in all the saprophytic water vibrios. It is affirmed that the O agglutinin is all-important. Evidence is accumulating that the O groups of vibrios are responsible for most of the serious outbreaks of cholera. Therefore, it is important that sera from cholera cases should be tested for O agglutinins.

Differential diagnosis.—True cholera may have to be differentiated from *ptomaine*, or *mushroom* poisoning, which may simulate it very closely, but in this instance there is usually a history of several persons having been attacked at the same time, after having partaken of a particular article of food, especially tinned. Leucocytosis is absent in food-poisoning though usually found during the early stages of cholera.

For the differential diagnosis of cholera from food poisoning, *see* Table VI, p. 459).

Algid or choleraic subtertian malaria may simulate true cholera very closely (*see* p. 69) ; *acute bacillary dysentery* may occasionally be so sudden and severe in its onset as to resemble cholera ; acute trichinosis is distinguished by leucocytosis and pronounced eosinophilia ; in *arsenical poisoning* vomiting is more usually the most urgent commencing symptom. Children suffering from cholera are apt to develop hyperpyrexia with cerebral manifestations, which may be mistaken for meningitis.

TREATMENT

During cholera epidemics it is customary to establish depots where sedative and astringent remedies for the treatment of diarrhœa are dispensed gratuitously. Chlorodyne in small doses, 10–15 drops, has been found to be of value in allaying the more urgent primary manifestations.

In the early stages of evacuation opium is of undoubted value. A hypodermic injection of morphia, $\frac{1}{4}$ gr. with atropine gr. $\frac{1}{100}$, should be given immediately. An anti-diarrhœic of value is as follows :

℞	Sodii bicarb.	gr.xv	(0·972 grm.)
	Cret. prep.	gr.xv	(0·972 grm.)
	Spirit. æther.	♏xv	(0·88 c.c.)
	Spirit. ammon. aromat. . . .	♏xv	(0·88 c.c.)
	Tinct. opii	♏xxx	(1·77 c.c.)
	Aq. chlor, ad.	℥i	(28·4 c.c.)

Of this, 1 fl. oz. should be given every twenty minutes until purging and vomiting cease.

Kaolin, or " bolus alba," as an intestinal astringent in large doses, adsorbs toxins, thus rendering them inert. It consists of kaolin[1] 200 grm.

---

[1] Kaolin powder suitable for this purpose may be obtained from the Electric Osmosis Co.

TABLE VI

	CHOLERA	FOOD POISONING
Diarrhœa.	Often associated with griping. Precedes vomiting.	Associated with some intestinal pain. Follows vomiting.
Vomiting.	Causes no distress. Watery and projectile; follows diarrhœa.	Often violent and distressing. Vomit consists of food and is never watery. Copious or projectile. *Generally precedes diarrhœa.*
Nausea.	Absent.	Constant.
Retching.	Rare.	Constant, often severe.
Abdominal pain.	Not usually severe.	Constant.
Tenesmus.	Absent.	Common.
Stools.	Watery and copious.	Liquid, fæcal, and offensive. Never colourless and copious.
Urine.	May be completely suppressed.	Never suppressed.
Muscular cramps.	Constant and severe.	In very severe cases confined to extremities.
Collapse.	Frequent. Chiefly from loss of fluid.	Faintness and syncope from toxæmia.
Fever.	Surface temperature below normal, but rectal temperature may be raised.	Axillary temperature 99–109° F.
Headache.	Absent.	Frequent.

(7 oz.) in 400 c.c. (14 oz.) of water. This is a single dose, but if there is vomiting it may be repeated, and sipped in small amounts at a time. It is inconvenient to administer on a large scale, on account of the bulkiness of the dose.

It has been shown that the adsorption-rate by kaolin is much more rapid in the case of the cholera vibrio than with an emulsion of equal strength of typhoid. Rapid adsorption is one of the reasons why kaolin in massive doses is beneficial in the treatment of cholera.

Subsidiary measures.—The patient should be kept strictly in the horizontal position, in a warm bed, and in a well-ventilated, but not too cold room. Thirst should be treated by sips of iced water, soda-water, champagne, or brandy and water. Copious draughts, as they are likely to provoke vomiting, are usually condemned. It does not follow from this that they are harmful; the emesis contributes to the elimination of toxins.

Cramps may be relieved by gentle frictions with the hand, by a small hypodermic injection of morphia, or, these failing, by chloroform inhalations.

The surface heat is maintained by hot-water bottles or warmed bricks placed about the feet, legs, and flanks. The patient must not be allowed to get up to pass his stools; a warmed bed-pan should be provided for this purpose. The foot of the bed should be raised. All food should be withheld while the disease is active.

Intravenous salines.—For the stage of collapse, which is due to the loss of a large amount of fluid, intravenous injections of salines must be resorted to in order to restore the balance. Collapse in cholera does not differ fundamentally from that due to hæmorrhage, and similar principles of treatment underlie both. Intravenous injection of normal saline is therefore indicated, but success appears to depend on the introduction of a sufficient quantity. Three to four pints may be necessary. Cox of Shanghai had encouraging results from continuous, prolonged, slow intravenous injections of isotonic saline fluid given by a special apparatus placed 2½ ft. above the level of the patient's arm. The flow is kept up for several hours, at a rate of 2 oz. per minute, as long as there is danger from collapse.* The saline injections may be combined with 5 per cent. glucose, which may act beneficially in urinary suppression. Normal saline was preferred as a routine in Hong Kong, because hypertonic salines were not successful. Ride (1938) considered that, until the nature of the fluid loss in cholera has been ascertained, it is better and more scientific to make good the dehydration loss by normal saline infusions. Recent experiences indicate that intravenous injections of plasma (or reconstituted plasma), in addition to normal saline, are physiological and beneficial. Should the veins be difficult to penetrate, transfusion may be performed into the peritoneum or under the breast. After introduction of two to four pints of saline into the peritoneal cavity, the veins soon become prominent, and intravenous injection can then be carried out.

Treatment of hyperpyrexia.—During the saline infusion, half-hourly charts of the rectal temperature should be kept and, should hyperpyrexia supervene, ice-packs must be applied and iced injected *per rectum.*

Rogers's treatment.—Though modern therapeutists regard this method as being based upon faulty physiological reasoning, it is necessary to give an outline of the data. Rogers, believing that collapse in cholera was due to excessive loss of chlorides from the blood-stream, introduced the intravenous *hypertonic* saline treatment. This is composed as follows: sodium chloride, 120 gr.; potassium chloride, 6 gr.; calcium chloride, 4 gr.; sterilized water, 1 pint. The fluid in the containing bottle should be at a temperature of about 100° F. if the rectal temperature is below 99° F.; if the latter is above 100° F., as there is risk from hyperpyrexia, the injection should be given at a temperature between 80° and 90° F. This solution is introduced by means of a special stopcock cannula and transfusion bulb at the rate of not more than 4 oz. a minute, the flow being slowed down to 1 oz. if distress or headache supervenes. From three to six pints should be run in, if possible. On an average, fifteen minutes should be taken for two pints of fluid. At the same time, potassium permanganate in solution or in pill by mouth up to 50 gr. a day is given in order to destroy toxins formed in the alimentary canal—2 gr. every quarter of an hour for two hours, then every half-hour until the stools are coloured green. These pills are made up in some inert material, such as kaolin and vaseline, without the addition of any oxidizable substance. They are coated with salol, in the proportion of one part to five parts of sandarach varnish.

With intravenous saline Rogers combined hypodermic injections of atropine, $\frac{1}{100}$ gr., morning and evening. The principles of the treatment are as follows:

A blood-pressure below 70 mm. of mercury indicates a dangerous collapse, and a specific gravity of the blood of 1063 or over indicates a loss of half the fluid from the blood. In the acute stage the specific gravity of the blood varies between 1060 and 1072, the normal figure for a European adult being 1058 and for an Eastern native 1056.

The specific gravity of the blood is estimated by employing a series of small bottles of aqueous glycerin with specific gravities increasing by 2° per bottle from 1048 to 1070. The specific gravity may be controlled by a urinometer. Blood from the patient is dropped on to the surface of the fluid in the bottles by a capillary pipette. The drop which remains stationary in the centre of the glycerin solution of a given strength indicates its specific gravity.

In the stage of collapse, anuria often occurs, and every effort must be maintained to re-establish the blood-pressure. Pituitary extract, or pitressin, is often useful during the stage of reaction, given in doses of $\frac{1}{2}$ to 1 c.c., hypodermically, two to four times a day; adrenalin may also be given, but its action is more transient. Caffeine citrate, 5 gr., is useful as a cardiac tonic and as a diuretic; it may be given three or four times during the twenty-four hours. Tincture of strophanthus, 5 min., three times a day, is useful as an adjuvant. In cases of complete suppression, dry-cupping over the lumbar region twice daily by Fenwick's cups may help to re-start the flow of urine, and may be supplemented later by hot dry fomentations. Rectal injections of hyperalkaline saline—150 gr. of sodium bicarbonate to the pint of isotonic saline—should be administered slowly every 2–4 hours in cases where collapse has been overcome but suppression of urine persists. The objection to using sodium bicarbonate is that this salt has a lytic action on the red cells *in vitro*, but in 4·5 per cent. concentration it has no hæmolysing effect. During sterilization the bicarbonate tends to be converted into the carbonate, but Sellards found that this tendency was minimized by sterilization in an autoclave connected with live steam at 7-lb. pressure.

If the secretion of urine is not quickly restored, large hot poultices or dry-cupping over the loins, and the judicious use of bland diuretics should be tried. Injections of digitalin, $\frac{1}{100}$ gr., may be given to stimulate the cardiac action.

During the stage of reaction, should purging persist, large doses of salicylate of bismuth with a little opium may prove of service.

Cholera typhoid must be treated much as ordinary enteric fever.

In cholera convalescents the diet for a time must be of the simplest and most digestible character—diluted milk, barley-water or rice-water, thin broths, meat juice, and so forth—the return to ordinary food being effected with the greatest circumspection.

Essential oils.—A popular treatment in India is an essential-oils mixture as follows:

℞ Spirit. æther.	. . . . . .	♏xxx	(1·176 c.c.)
Ol. anis.	. . . .	♏v	(0·296 c.c.)
Ol. cajup.	. . . .	♏v	(0·296 c.c.)
Ol. junip.	. . . .	♏v	(0·296 c.c.)
Acid. sulph. aromat.	. . . . .	♏xv	(0·888 c.c.)

Half a drachm (1·176 c.c.) in half an ounce of water, every quarter of an hour Total dose, 8–14 drachms.

This mixture should be given immediately, when practicable, and it is claimed that vomiting, purging, and intestinal pains are controlled. The value of the method in mass treatment is obvious, as little supervision is requisite.

Sulphaguanidine.—Chopra and colleagues first reported on this treatment in cholera. The dosage to an average Indian patient in this series was 5 grm. on admission, and 2·5 grm. every four hours until a total of 20 grm. had been given. The mortality rate was 3·21 per cent. Others have not found sulphaguanidine of any value, even when combined with intravenous hypertonic saline.

Bacteriophage.—Asheshov, Khan, and Lahiri gave bacteriophage together with intravenous hypertonic saline. Sterilization is done under pressure in the autoclave (30 minutes at 120° C.) and not by boiling. Three pints of hypertonic saline are given intravenously, together with an additional pint of alkaline salt solution (150 gr. sodii bicarb. to a pint of normal saline). Together with this the cholera bacteriophage is given undiluted by the mouth in one drachm doses every 30 minutes, or 5 c.c. intravenously for more rapid action. The results have not been impressive.

Anticholera serum.—Ghosh and others tried injection of a new anticholera serum of an increased potency. This has been produced by a modification of toxin production with the object of obtaining a maximum quantity of both endo- and exotoxin. The serum is best injected intraperitoneally in doses of 70–80 c.c. The results are stated to be encouraging, and it was found that, in cases with a blood specific gravity of 1064 or more, the mortality was reduced by more than 50 per cent. No cases of uræmia occurred in the series. The intravenous injection of the serum is by no means so favourable as the intraperitoneal.

Mortality-rate.—The death-rate for cholera has always been high. In former days in India it was seldom less than 70 per cent. In the decade ending 1908 it was 54·2 per cent. in Indian and 78·5 per cent. in British troops in India. With improved methods of treatment it has declined, but is still about 20 to 80 per cent. The death rate in collapsed cases is considerably higher, and, even with modern methods, remains about 65 per cent.

The prognosis is unfavourable in those over fifty years of age and in children under five.

Prophylaxis. *Quarantine prevention.*—Theoretically, quarantine should be an efficient protection against the introduction of cholera into a community; practically, it has proved difficult to apply. Unless they are stringent and thoroughly carried out, these regulations can be of little use. Even if the utmost care, intelligence, and honesty succeed in excluding individuals actually suffering from cholera, or likely within a reasonable time to suffer from it, there is yet no guarantee that the germ of the disease may not be introduced. Convalescent patients may pass vibrios in their stools. For the recognition of the carrier state it is necessary to examine the stools of all contacts. A small dose of calomel to clear out the contents of the small intestine greatly increases the chance of recovering the specific organism from stools. This is the only scientific method of conducting a reliable quarantine.

The system to which Great Britain apparently owed her immunity during epidemics on the continent of Europe is a practicable and, in civilized conditions, an efficient one. Under this system, only ships which were carrying or which had recently carried cholera patients were detained ; and even these merely until they could be thoroughly disinfected. Thus, inconvenience and loss to travellers and merchants were small, and the temptation to conceal cases of the disease or to evade regulations was proportionately minimized. Any cholera cases were isolated in suitable hospitals, the rest of the crew and passengers, although supervised for a time, being given free pratique. At the same time attention was not diverted from the sanitation of towns, especially of seaports—the measure mainly relied upon. Suspicious cases occurring on shore were at once reported to the sanitary authorities and promptly dealt with, fomites being destroyed or disinfected at as little cost and inconvenience to individuals as possible. Every endeavour was made to prevent fæcal contamination of the public water supply.

Of late years, in India, preventive measures have been conducted much on the same lines, attention being given to sanitation rather than to quarantine. During the great religious festivals the sanitary condition of the devotees is looked after as far as practicable, special care being given to provide them with good drinking and bathing water. On the appearance of cholera in the vicinity of troops in India, special protective measures are promptly instituted, elaborate directions having been drawn up for the guidance of medical officers.

Wells and water supplies during a cholera epidemic should be treated with potassium permanganate until the water becomes pink ; an appropriate strength is 60 gr. to the gallon of water. The water should not be used until it has been colourless for twenty-four hours, and all vegetation and aquatic fauna removed.

It is held in India that one of the major measures of prevention is the provision of safe permanent water supplies to the whole population.

The application of bacteriophagic principles to sanitation.—According to Graham and Morison, choleraphage is absent in the intestinal tract before the beginning of a cholera epidemic. Little or no phage is found in the first victims to be stricken, and this substance is elaborated as the epidemic progresses, so that those patients who develop a rapid exaltation of choleraphage recover. Thus, this factor can be used as a prophylactic measure in disinfecting wells. For this purpose 30 c.c. of potent bacteriophage were added to two wells in the contaminated area. One case only developed in those who drank this water.

Haffkine's inoculation.—During the 1914–1918 war many millions of anticholeraic inoculations were made. The initial dose is ½ c.c. of an emulsion of 4,000 millions, followed seven to ten days later by a second inoculation of 1 c.c. containing 8,000 millions. Experience has shown that even larger doses can easily be tolerated. Local reaction is, generally speaking, very mild. There may be œdema and a painful infiltration at the site of the injection, rarely followed by systemic disturbance.

Several strains of cholera vibrios are used. They are inoculated into Roux bottles containing "pea-extract agar" and grown for forty-eight hours. The growth is washed off with normal saline, and the emulsion counted, with dark ground illumination. The emulsion is then heated to 55° C. for one hour, after which 1 per cent. carbolic is added. The emulsion thus sterilized is finally diluted down so as to contain 8,000 million vibrios per c.c. of saline and 0·5 per cent. carbolic.

The immunity thus produced does not seem to be very persistent, lasting at the maximum for three or four months.

Experience, particularly that obtained during the Balkan War in 1913, in Batavia in 1915 and 1916, and in the 1914–18 war, has gone far to confirm the earlier impressions of the value of Haffkine's inoculation.

In India from 1905–1916 the annual number of deaths attributed to cholera was never less than 300,000. Epidemics of cholera are readily controlled by vaccine when inoculation is made compulsory; thus, when this disease was introduced into Korea from China in 1926, the outbreak was promptly brought to a close by the inoculation of more than one million persons.

Immunization per os.—(Besredka). The vaccine is made from thick suspensions of the organisms killed by heat, carbolic acid, or alcohol, and given in from 3 to 5 doses ranging up to 100 c.c. every other day. Each dose consists of 10–100 milliards of vibrios, or 0·01–0·1 grm. of the dried organisms. The full course of bili-vaccine, as it is called, is said to confer the same degree of immunity as ordinary vaccine, but that produced by a simple inoculation is probably as high as that afforded by a full course of bili-vaccine.

Personal prophylaxis.—During cholera epidemics great care should be exercised to preserve the general health; at the same time, anything like panic or apprehension must be sedulously discouraged. Visits to cholera districts should be postponed, if possible, seeing that the newcomer is especially liable to the disease. Unripe fruit, over-ripe fruit, shell-fish and food in a state of decomposition should be avoided. All drinking-water, and all water in which dishes and everything used in the preparation and serving of food are washed, should be boiled. Mere chlorination of the water with bleaching powder ($CaOCl_2$), giving 1·3 parts of chlorine per million, or added to water in the proportion of 2 grm. of the powder to every 110 gallons, is not entirely reliable. Sodium bisulphate tablets (2 grm. to 1¾ pints of water), by liberating sulphuric acid, provide a most useful method of sterilizing water for personal use, as for instance in a water-bottle. Filters—except perhaps the Pasteur-Chamberland—are not for the most part to be relied upon; in many instances they are more likely to contaminate the water passed through them than to purify it. A good plan in a household or in public institutions is to provide for drinking purposes an abundant supply of weak tea or lemon decoction, the supply being renewed daily; such a plan ensures that the water used in the preparation of the drink has been boiled. All food should be protected from flies. Diarrhœa occurring during cholera epidemics should be vigorously treated.

CHAPTER XXVIII

THE DYSENTERIES AND LIVER ABSCESS

THREE types of dysentery, correlated to three quite distinct and, zoologically, widely separated parasites have now been definitely established. Though of a totally different ætiology they are not mutually exclusive, for one type may be superimposed upon and complicate another; moreover, any or all of them may be implanted on some general disease, such as malaria or typhoid. The term "dysentery" denotes a symptom-complex, but does not indicate some particular disease of distinct ætiology. It is most important that a sane and critical view should be taken on the all-important matter of differential diagnosis of the dysenteries as there are many pathological conditions of the intestines which may give rise to a discharge of blood and mucus, but which are not connected with any particular parasitic infection.

The principal forms of dysentery and their respective parasites are as follows:

I. BACTERIAL—
- THE BACILLARY DYSENTERIES:
  - *Bacterium dysenteriæ*—Shiga, Schmitz, Flexner and Sonne.

II. PROTOZOAL—
- AMŒBIASIS—Amœbic dysentery, Liver abscess, etc.
  - *Entamœba histolytica.*
- BALANTIDIAL DYSENTERY:
  - *Balantidium coli.*

III. HELMINTHIC—
- BILHARZIAL DYSENTERY:
  - *Bilharzia mansoni, B. hæmatobia, B. japonica.*
- VERMINOUS DYSENTERY:
  - *Œsophagostomum apiostomum,* or *Œ. stephanostomum.*

I. BACILLARY OR EPIDEMIC DYSENTERIES

EKIRI—Japanese

Definition.—Acute epidemic diseases due to invasion of the mucosa of the large intestine by specific bacilli (*B. dysenteriæ* Shiga, Schmitz, Flexner, or Sonne). Pyrexia, symptoms of toxic absorption, and the discharge of blood-stained mucus in the stool usually occur. In severe cases coagulation necrosis of the mucosa may take place and quickly lead to death. In the milder forms the clinical symptom may be a simple diarrhœa.

Geographical distribution.—Epidemics of bacillary dysentery are frequent both in the tropics and in temperate countries. At present such epidemics are of greater intensity and frequency in those countries in which the insanitary habits of the natives and more primitive conditions of life lend themselves to the spread of disease. In mediæval times bacillary dysentery epidemics seem to have been much more widespread and virulent when the sanitary conditions were more akin to those among primitive tropical natives. In Europe, bacillary dysentery is mainly an institutional disease, occurring not infrequently in lunatic asylums, prison camps, and military barracks. In the Gallipoli campaign (1915) it was responsible for the majority of the 120,000 medical casualties evacuated within three months. Sonne dysentery has been widespread, especially in children, during recent years, during the winter months, in England, Europe and America.

Epidemiology.—In the tropics and subtropics, the bacillary dysenteries appear to observe a definite seasonal incidence. They are certainly prevalent during the rainy season and for a short subsequent period, but mostly in the autumn months, while minor epidemics may also be noted in the early spring. During the hot dry African summer they are in abeyance. Epidemic dysentery is associated with the rainy season in the tropics for the following reasons. The rains deter people from defæcating at a safe distance from the village; waterlogging of the soil prevents the bacilli from dying out; people are more liable to chills, which often cause an acute attack; natives crowd together, which increases the chances of infection, together with an increased risk of pollution of water supplies. The infection spreads rapidly from man to man.

Bacillary dysentery has always been a scourge of war. If we may trust the records of history it was an important factor in the Napoleonic wars, in the Franco-Prussian War of 1871, and in the South African War of 1899–1902. Large epidemics of bacillary dysentery occurred during the war of 1914–18, and as a cause of invaliding it was hardly secondary to any other disease. In the Middle East, India, Iraq and East Africa the general tendency was to mistake, for reasons pointed out on p. 478, amœbic for bacillary dysentery. That bacillary dysentery was the predominating form in every epidemic of war dysentery from the Gallipoli campaign onwards was pointed out by the Editor and others. This has been borne out by the experience of the present war.

Direct contagion by fæces occurs, as a rule, among primitive communities in which the ordinary sanitary observances are either unknown or disregarded. The spread of dysenteries in lunatic asylums and Indian bazaars is attributable to personal habits which lend themselves to dissemination of infection. Contamination of food by the soiled hands of carriers, especially Army cooks, and contamination of vegetables by use of human nightsoil as a fertilizer are also possibilities.

Indirect contagion. (*a*) *Flies.*—There appears to be little doubt that houseflies (*Musca domestica*) commonly act as carriers of the infection. The seasonal incidence of bacillary dysentery corresponds in a remarkable manner with the maximum prevalence of these pests. In 1910 the Editor demonstrated Shiga dysentery bacilli, in considerable numbers, in the intestinal tract of houseflies in an endemic area. This work was confirmed by Taylor and others. The housefly is able to spread dysenteric infection firstly, by regurgitation preparatory to feeding on food; and secondly (probably more commonly) by its fæces. Buxton found that the intestinal canal of the majority of houseflies caught in Iraq contained human fæces.

The importance of the insect in the spread of the bacillary dysenteries can therefore be understood.

(*b*) *Water* acts as a medium of infection, especially in the Dutch East Indies and Malay States. It has been shown that the bacillus can survive in drinking-water for over three weeks, but not for so long when exposed to the sun or when associated with numbers of putrefactive micro-organisms.

(*c*) *Milk.*—Several outbreaks of Flexner and Sonne dysentery in southern England and in Europe have been ascribed to contaminated milk.

(*d*) *Food.*—Sonne dysentery is a food infection and should be classified among the group of food-poisonings. One of the largest outbreaks in London in 1933 was ascribed to eating " pease pudding."

(*e*) *Susceptibility of the individual.*—New arrivals in the tropics are liable to this form of dysentery, and small children are specially so. Patients whose resistance has been undermined by intercurrent disease, such as malaria, pellagra and tuberculosis, are apt to die from terminal bacillary dysentery.

(*f*) *Carriers* (*see* p. 477).

Ætiology.—*Bact. dysenteriæ* was discovered by Shiga in 1898, confirmed two years later by Kruse in Germany. It has therefore been known as the Shiga-Kruse bacillus.

Shiga's bacillus is a rod-shaped Gram-negative organism, 1 to 3 μ in length by 0·4 μ in breadth ; it is non-motile, and often exhibits very active Brownian movement. Vedder and Duval have demonstrated numerous lateral flagella of great tenuity. On agar and gelatin it grows as a thin smooth film with regular margins, and on MacConkey plates its colonies much resemble those of the typhoid bacillus ; they are regularly round, light-blue and dew-like. It produces no liquefaction of gelatin, and grows as a transparent, almost invisible, layer on potato. With solutions of the sugars (*see* Table VII, p. 468) it produces acidity in glucose, but is inert in the rest of the series and does not produce indol in peptone water. The organism is agglutinated in high dilutions by the serum of patients suffering from the disease. It occurs in considerable numbers in dysenteric lesions, and in the mucous stools of the corresponding period of the disease.

A variety of Shiga's bacillus (resembling that organism in its sugar reaction, *but forming indol* and not agglutinating with Shiga-immune serum) is known as Schmitz's bacillus and has been shown to be of considerable importance in the Middle East. (This organism is identical with *B. ambiguum* of Andrewes.)

Cultures of *Bact. shigæ* are toxic to laboratory animals, especially rabbits, but in these animals they do not produce lesions characteristic of dysentery, though filtered toxins, when injected intravenously, cause necrosis of the large intestine. In two experiments in man, one intentional, the other accidental, ingestion of pure cultures was followed, within a short time, by well-marked symptoms of dysentery.

Flexner's bacillus (the Flexner-Boyd group).—In 1900 an organism morphologically similar to Shiga's bacillus, but differing in the production of acid from mannite as well as glucose, producing indol from peptone somewhat irregularly, and inagglutinable with Shiga-immune serums, was isolated by Flexner from cases of dysentery in Manila. From the work of Andrews and Inman on a very large number of strains of Flexner—*the mannite-fermenting group*—it can be definitely stated that the organism does not adhere to one constant type, as does Shiga's bacillus, but differs greatly in the toxicity of the various strains and in their

TABLE VII.—BIOLOGICAL REACTIONS OF PATHOGENIC AND ALLIED ORGANISMS RECOVERED FROM THE FÆCES

	Mannite		Glucose		Maltose		Lactose		Saccharose		Dulcite		Litmus or Phenol Red Milk			Indole	Motility
	A	G	A	G	A	G	A	G	A	G	A	G	A	Alk	Clot		
Bact. shigæ . . .	0	0	+	0	0	0	0	0	0	0	0	0	+	0	0	0	0
Bact. flexneri . . .	+	0	+	0	+	0	0	0	0	0	0	0	+	+	0	+	0
Bact. ambiguum (*Schmitz's bacillus*) . . .	0	0	+	0	0	0	0	0	0	0	0	0	+sl	0	0	+	0
Bact. Sonnei . . .	+	0	+	0	0	0	+	0	+ or 0	0	0	0	+	0	+	0	0
Newcastle bacillus . .	±	0	+	+sl	+	—	—	—	—	—	+	—	+	+sl later	—	—	+
Bact. morgani . . .	0	0	+	+sl	0	0	0	0	0	0	0	0	0	+	0	+	+
Bact. typhosum . .	+	0	+	0	+	0	0	0	0	0	0	0	+	0	0	0	+
Bact. paratyphosum A. .	+	+	+	+	+	+	0	0	0	0	+	+	+	0	0	0	+
* *Bact. paratyphosum B.* .	+	+	+	+	+	+	0	0	0	0	+	+	+	+	0	0	+
* *Bact. enteritidis* . .	+	+	+	+	+	+	0	0	0	0	+	+	+sl	+	0	0	+
Bact. coli . . .	+	+	+	+	+	+	+	+	0	0	+	+	+	0	+	+	+
Bact. acidi lactici (*Hüppe*) .	+	+	+	+	+	+	+	+	0	0	0	0	+	0	+	+	0
Bact. fæcalis alkaligenes .	0	0	0	0	0	0	0	0	0	0	0	0	0	+	0	0	+

A = acid. G = gas, Alk = alkaline, Sl = slight.

* To differentiate *Bact. enteritidis* and other organisms of the food-poisoning group from *Bact. paratyphosum B.* serological tests must be applied.

antigenic properties. The basis for satisfactory sub-grouping was established by the serological method of Murray, Andrewes and Inmàn. It appeared that five definite strains of the bacillus could be identified, known respectively as V, W, X, Y, Z, and for their recognition five specially prepared homologous serums were necessary. The more recent study (Boyd, 1938) of antigenic variation among mannite-fermenting dysentery bacilli suggests that loss in culture of *type-specific* antigen, which is not shared by other members of the group, is associated with an increase, real or apparent, of non-specific *group* antigen. A different explanation of the observations of Andrews and Inman is thus put forward. It seems probable that available cultures of the historical Hiss and Russell Y are degenerate variants of an original W strain, and that an Indian strain, 103A, is actually the type-specific Flexner-Y. This has been found to be fairly common, both in the United Kingdom and in other parts of the world (W. M. Scott, quoted by Boyd). This work emphasizes the great importance of using type-specific suspensions in diagnostic agglutination tests. Stock Flexner-Y strains may on these grounds be almost or quite devoid of type-specific antigen.

The Newcastle bacillus, first recognized as a cause of dysentery by Clayton and Warren, corresponds to Boyd's No. 88. It has now been found in other parts of England, India and Nigeria. Owing to the fact that it forms small quantities of gas in solution of the sugars and is motile on first isolation, it frequently escapes detection.

Sonne's bacillus (*Bacterium dysenteriæ sonnei*) which ferments lactose slowly, is responsible for outbreaks of enterocolitis in Egypt and elsewhere (Perry), and may produce symptoms of food poisoning resembling those of the *Salmonella* group. The importance of this infection has been recognized in England and in America during recent years as a cause of dysentery and diarrhœa of definite seasonal occurrence, especially in children. The colonies of this bacillus tend to assume a much more crenated outline than do those of the Flexner type, but are usually larger than those of Shiga or Flexner on MacConkey's medium. Cultures of Sonne's bacillus are not agglutinated by standard Flexner or Shiga sera. When titrated against a specially prepared Sonne anti-serum, agglutination to full titre occurs. Often, however, when freshly isolated, the bacillary emulsion is inagglutinable, but will abstract the agglutinins from Sonne serum by absorption. On MacConkey's medium, Sonne colonies frequently show a small central point of acidity on a somewhat opaque background. Sonne's bacillus is indol-negative and zylose-negative. It ferments glucose and mannite in twenty-four hours, and lactose and saccharose after some days. Serological varieties and strains are now recognized. Though not so toxic as Shiga's bacillus, Sonne's bacillus, when injected into rabbits, may produce sudden death.

Dysentery bacilli can be isolated from the intestinal canal and the mesenteric glands. The organisms have also rarely been obtained from the blood-stream, gall-bladder and joint-effusions. Selective cultivation media, especially for Flexner and Sonne bacilli, have been introduced to render their isolation easier. The best is Leifson's desoxycholate-citrate medium (Haynes' modification).

Apparently both the Shiga and Flexner bacilli are encountered in sporadic cases and in some epidemics without a preponderance of any one particular type ; but it may be stated that Shiga's bacillus is more frequent in the tropics than in temperate zones, and is responsible for the most severe clinical forms of the disease, and consequently for the most virulent epidemics.

Toxins.—The O forms of *Bact. shigæ* contain both exo- and endotoxins. The former is insoluble in dilute trichloracetic acid, whilst the endotoxin can be precipitated from watery solution by means of alcohol or acetone, after removal of the acid by dialysis, yielding 10 per cent. of dry weight of the organisms. There are said to be two endotoxin fractions which are distinguishable by their nitrogen content and toxicity. Adsorption is effected by aluminium hydroxide. The endotoxin appears to be a large molecule complex of phospholipoid-carbohydrate-polypeptide. The chemical properties of the exotoxin are those of a protein. It is thermolabile and its capacity to combine with antitoxin can be measured by its flocculation reaction. Formalized toxoid can be prepared from it, but not from the endotoxin. Exotoxin can be concentrated by ammonium sulphate fractionation. The properties of different dysentery toxin preparations depend upon origin, strains and methods of preparation (Wagner-Jauregg and Helmert, 1942).

Pathology.—The primary lesions of bacillary dysentery (Shiga and Flexner infections) are confined to the solitary follicles of the large intestine, and result in a sinuous " snail-track " ulceration of the folds of mucous membrane. In very acute cases the process consists of intense hyperæmia of the large intestine, which eventually culminates in necrosis of the mucosa of the entire colon, as well as of the last 2–3 ft. of the ileum. Exceptionally, the whole of the mucosa of the small intestine may be involved.

As a general rule, the lesions characteristic of bacillary dysentery are most pronounced in the lower part of the intestinal canal, from the sigmoid flexure to the anal canal. In the stage of *necrosis* the large gut is contracted so as to resemble a stiff tube, and the mucous membrane is converted into a rigid, resistant, olive-green or blackish substance (Plate X, Fig. 3). The colour is thought to be due to the staining of the dead tissue by bile-pigments. Occasionally, this necrosis may have a patchy distribution affecting especially the descending and pelvic portions. There are many signs of acute toxæmia.

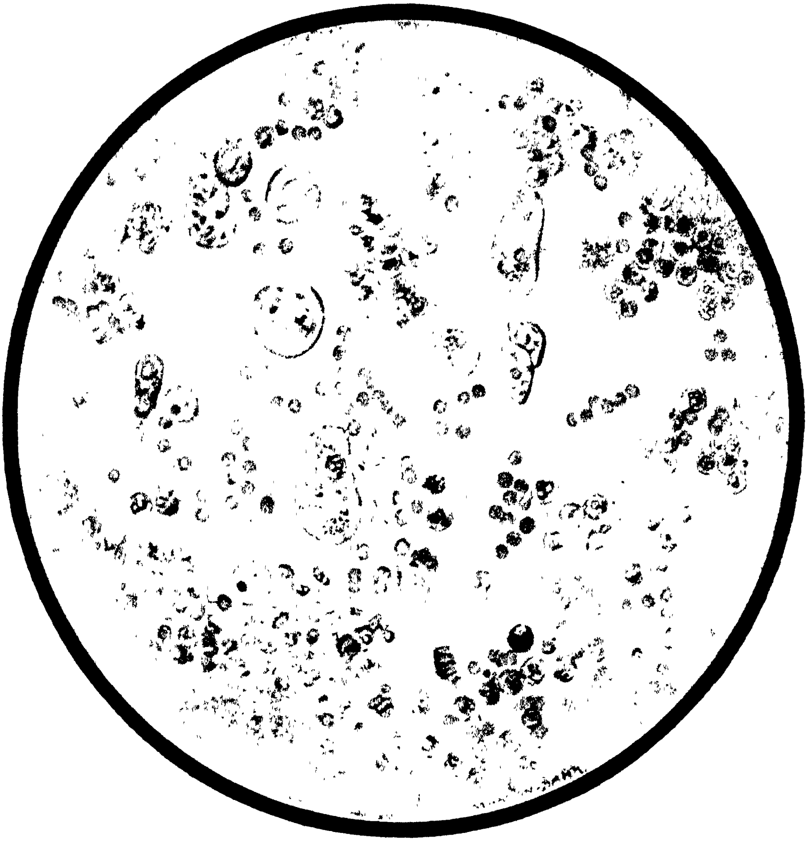
When the necrotic patches have a more local distribution, irregular ulcers, often communicating with one another by submucous sinuses, form and may involve the entire wall; such a bowel surface has a fenestrated appearance. Inflammatory changes are found in the mesenteric glands, with macrophage activity.

Chronic ulceration of the large gut may occur in bacillary dysentery. The smallest lesions are lenticular and involve the mucous surface alone. The more advanced lesions amount to ulceration of limited tracts of mucous membrane, rarely penetrating beneath the muscularis mucosæ. Ante-mortem perforation of the gut may supervene, though it is rare. For the differentiation of these ulcers from those of amœbic dysentery the reader is referred to Table VIII, p. 481.

These ulcers must also be distinguished from those of tuberculous, typhoid, or bilharzial origin, and also of ulcerative colitis. In some chronic cases the mucous membrane may be entirely destroyed, rendering recovery impossible. The gut then resembles a piece of chamois-leather with interlacing fibrotic strands on the surface.

Mucous retention cysts, due to the formation of pseudo-adenomata from the bases of Lieberkühn's follicles, may sometimes be found as a sequela of bacillary ulceration, as first described by the Editor. They may be recognized as jelly-like elevations forcing up the mucous surface and scattered throughout the length of the large gut. Dysentery bacilli may be isolated from their contents, and they are present in the large intestine of " carriers " of bacillary dysentery (Fletcher and Jepps.

Granulation tissue.—Many cases of chronic bacillary dysentery acquired in the 1914–18 war showed no ulceration, but a granular condition of the mucous membrane of the large gut. The lesions are distributed, as a rule, irregularly, usually confined to the lower portion. Considerable infiltration of the walls of the gut is associated with this condition. As in ulcerative colitis, stenosis of the



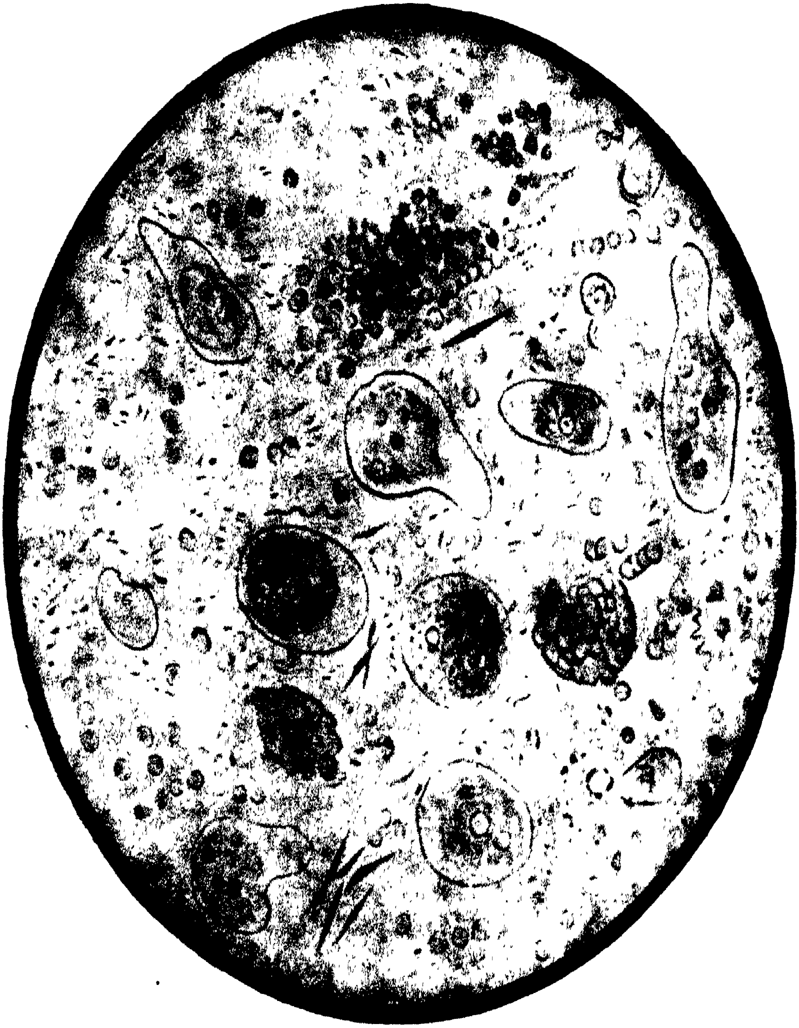
(P. H. Manson-Bahr, del.)

MICROSCOPIC APPEARANCE OF CELLULAR EXUDATE IN ACUTE BACILLARY DYSENTERY (Shiga infection).

Fresh preparation. Shows macrophage cells with ingested red blood-corpuscles, intestinal epithelium and polymorphonuclear leucocytes.

PLATE XI

AB SALAR JUNG BAHADUR



(*P. H. Manson-Bahr, del.*)

MICROSCOPIC APPEARANCE OF EXUDATE IN AMŒBIC DYSENTERY.

Fresh preparation. Shows active *Entamœba histolytica*, some with ingested red blood-corpuscles; acicular Charcot-Leyden crystals and disintegrated intestinal epithelium.

PLATE XII

large intestine, either localized or general, may take place as a result. Mixed infection of amœbic and bacillary dysentery may be sometimes met. The spleen shows congestion of pulp and reticulo-endothelial activity. The kidneys in Shiga infections may show patchy glomerular congestion and catarrhal changes. In cases of longer duration the kidneys are enlarged and the convoluted tubules necrosed, with extensive cloudy swelling. Nephritis is often the cause of death (Dick, 1942). Emboli in liver and spleen occur.

Histopathology.—The submucosa is the seat of numerous hæmorrhages and of round cell-infiltration (Fig. 66). The ganglion cells of Auerbach's plexus are involved in perilymphatic inflammation. The formation of macrophage cells from the capillary endothelium of the vessels may also be observed. Owing to their large size, hyaline appearance, and vacuolated protoplasm, these cells, even in microscopic sections, are apt to be mistaken for *Entamœba histolytica* (Plate XI). These cells appear in an early stage in acute ulcers and in granulation tissue of chronic lesions.

The pathological appearances of Sonne dysentery are not so well known as are those of Shiga and Flexner infections. The changes are, on the whole, similar, but not by any means so severe (Plate X, Fig. 2).

Symptoms.—After a short incubation period, usually of from one to seven days (as ascertained by experiment) the disease begins in a variety of ways, suddenly or insidiously, in all degrees of severity from mild diarrhœa to an acute fulminating attack.

The main clinical symptoms are those of inflammation of the large intestine, viz., griping, tenesmus, frequent passage of loose, scanty, muco-sanguineous stools, often with dysuria.

The onset may be attended with high or moderate fever, or there may be no rise of temperature. The symptoms may be grafted on to some general disease such as scurvy or malaria, or to some chronic disease of the alimentary canal, as sprue; they may assume acute characters, or they may be subdued from the outset. As a general rule, the closer to the rectum the lesions are placed the more urgent the tenesmus; the nearer the cæcum the more urgent the griping. General constitutional symptoms due to the absorption of toxins may be evident. Vomiting may occur from the outset or be absent altogether.

Palpation of the abdomen is difficult during the early stages, owing to the rigidity of the recti muscles. Later, especially in toxic cases, the abdomen may become quite lax and the spastic sigmoid colon can be felt as an elastic cord. Implication of other portions of the large intestine can usually be detected from tenderness on pressure.

Blood changes.—There are few characteristic blood changes. As a rule, there is a polymorphonuclear leucocytosis of 16,000–30,000 at the commencement of the attack, falling to normal or subnormal on the third or fourth day.

Character of the stools.—At first fæcal and diarrhœic, the evacuations may vary enormously in number and character. Their number may be uncountable, the unfortunate victim being " glued to the commode." At first they consist of viscid blood-stained mucus, which has been compared to " red-currant jelly " or " frog's spawn," and are generally odourless. The characters by which they may be distinguished from amœbic fæces are given on p. 481. A few teaspoonfuls only may be passed at a time.

Subsequently they contain less blood and become more purulent. Finally, biliary pigments re-appear and the fæcal character may be re-established.

In the most acute and fulminating forms the mucus may contain a large proportion of altered blood and the evacuations resemble " meat washings." When necrosis of the mucosa has taken place the stools may be exceedingly offensive, grey, and contain much altered blood without mucus.

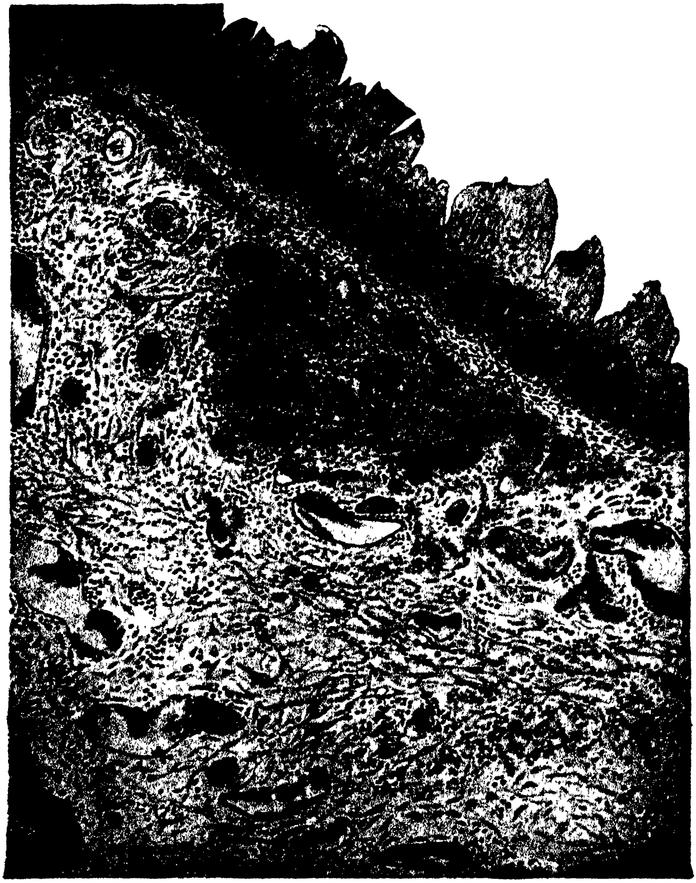


Fig. 66.—Microscopical section of large intestine in bacillary dysentery, showing necrosis of mucosa, cellular infiltration, and hæmorrhages into submucosa.

On clinical grounds, bacillary dysentery may be classified as follows :

1. *Mild or catarrhal bacillary dysentery.*—A common history is that for some days the patient had suffered from what was supposed to be an attack of diarrhœa. The stools, at first bilious and watery, perhaps four or five in the twenty-four hours, had latterly and by degrees become less copious and more frequent, less fæculent and more mucoid, their passage attended by a certain amount of straining and griping.

At the same time the tongue may remain clean, and there may be no accompanying pyrexia. The attack may be over in a week, and the stools may not number more than twelve in the twenty-four hours. The majority of these mild cases are due to Flexner, Schmitz or Sonne bacilli.

2. *Acute bacillary dysentery.*—In others the onset is much more abrupt. Within a few hours dysentery may be in full swing. The stools, at first fæculent, soon consist of little save blood-stained mucus. Very shortly the desire to stool becomes increased, the griping and tenesmus being accompanied, perhaps, by distressing dysuria. Fever, which at the outset may have been smart and preceded by rigor, subsides. The face is anxious and pinched: the cheeks are high-coloured from a toxic flush. Slight delirium and mental confusion may be added to the clinical picture. Thirst may be considerable, anorexia complete, and the tongue white or yellow-coated. In a week or more the urgency of the symptoms may diminish, and the attack tapers off into a subacute or chronic condition, or it may end as abruptly as it began (Chart 22).

3. *Fulminating bacillary dysentery.*—These are invariably Shiga infections. The attack generally begins suddenly, it may be in the middle of the night, with chills or smart rigor, vomiting, headache, and a rapid rise of temperature to 100° or even 104° F. Very shortly after the rigor, purging begins, the stools rapidly assuming dysenteric characters. In from two to three days up to a week or longer, vascular failure sets in with a subnormal temperature, and the patient dies, or the toxæmia may be so virulent that death may take place before dysenteric stools are passed. The tongue is thickly coated, and other signs of an acute toxæmia are present. The abdomen is sunken and acutely tender. The stools rapidly become liquid, offensive, and greenish or greyish. Towards the end, neither blood nor mucus may be visible in the almost uncountable evacuations.

A *choleraic* form, in some respects resembling cholera, has been noted. The onset is acute, with vomiting. Collapse with its attendant phenomena sets in early. The stools are liquid, serous, light-coloured, with blood and mucus flecks. The temperature is subnormal and death may take place within three days.

4. *Relapsing bacillary dysentery.*—In a proportion of bacillary dysenteries, although the urgency of the initial attack may subside, dysenteric symptoms do not completely disappear. The stools may recover their fæculent

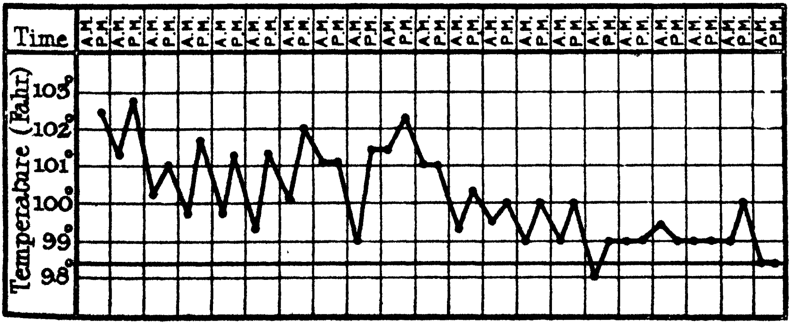


Chart 22.—Bacillary dysentery.

character, or may even show some signs of formation, yet they continue to be passed too frequently, often preceded by griping, and contain a variable amount of muco-pus, with or without blood. Cases of this type may be due either to a fresh, or to recrudescence of an old infection.

5. *Chronic bacillary dysentery.*—In quite a large proportion of cases of acute dysentery the fæces do not become absolutely normal for a considerable time after abatement of the more urgent symptoms. On the slightest indiscretion, the old symptoms re-appear, provoking unexpected attacks of diarrhœa. For months, or even years, some patients never pass a perfectly healthy stool, the unformed motion always containing muco-pus and at times blood. Often there is a tendency to scybalous stools, or to constipation alternating with diarrhœa.

Since the end of the 1914–1918 war a type of chronic bacillary dysentery has been quite common; it differs from any previously described. The initial attack may have been so mild that it has passed unnoticed, but recurrences take place, with passage of blood and mucus, becoming more frequent and intense as years go by. Eventually the stools resemble those of chronic ulcerative colitis.

The following varieties may be distinguished :—those with superficial ulceration from which the causative organism may be isolated by rectal swabs; those without actual ulceration, but with patches of granulation tissue in which cultures are negative; and finally those with generalized mucoidal inflammation and deep involvement of the bowel wall.

The course of these cases tends to be progressive, and, unless vigorously treated with sulphaguanidine they may terminate fatally. Emaciation may be extreme, especially in native races; an adult may weigh less than 49 lb. (Fletcher and Jepps.) Considerable anæmia may develop, with cardiac failure and dropsy. Death may ensue from exhaustion, or from some intercurrent disease, such as tuberculosis or malaria.

Bacillary dysentery in children.—Infection with dysentery bacilli (Shiga or Flexner) in small children, especially Europeans, may produce most acute and rapidly fatal symptoms. They may die in convulsions before the intestinal symptoms have had time to develop. The cases may resemble meningismus, and at the onset, on account of pyrexia and toxæmia, simulate enteric infections.

Post-dysenteric ascites.—Megaw is of the opinion that the ascites which is so common in most hospitals in India is a sequel to bacillary dysentery. When bacillary dysentery is not treated, or is improperly handled, the dysenteric toxins pass through the intestinal wall and set up an irritative peritonitis which is followed by fibrosis of the peritoneum. The result is ascites, which, according to Snapper, may be associated with liver cirrhosis. Massive serous intraperitoneal effusions, which may prove fatal, have been recorded from the Middle East.

Symptoms of Sonne dysentery.—In most cases mild attacks of dysenteriform diarrhœa are the rule. The fæces are greenish, or yellowish and offensive, with blood-flecked mucus from which the organism may be cultured. In the more acute attacks the symptoms more closely resemble those of Flexner dysentery, with sudden onset of colic, diarrhœa and, later, blood and mucus. Sometimes, however, they are still more acute, with pyrexia and vomiting, and may assume an alarming aspect reminiscent of salmonella infections. Then "tomato soup" stools are passed, followed by rapid prostration. Sonne infections are usually pyrexial at the time of the abrupt onset, but in the milder cases the fever is slight and transient. A feature is associated catarrh of the respiratory tract with diarrhœa. Rhinitis may precede the abdominal symptoms. Acute Sonne infections in children up to nine years of age may cause sudden death. Some observers believe that in this instance the symptoms are produced, not so much by the organisms, as by their toxins in contaminated food, which forms a favourable medium for their propagation. In mental institutions especially Sonne infections are apt to attack the inmates.

Cruickshank and Swyer found that, by repeated examination of fæcal specimens and rectal swabs, Sonne's bacillus could be isolated in most cases, and that the latter method gave a higher proportion of positive results. The Sonne bacillus persists in the intestine in a gradually decreasing proportion of cases after subsidence of the acute manifestations. Thus, the convalescent carrier becomes an important reservoir for its spread. Three consecutive negative laboratory reports should be obtained before the patient is released from hospital.

Predisposing causes.—Bacillary dysentery is especially apt to attack those who are in an enfeebled state owing to starvation, unsuitable dietary, physical exhaustion or exposure, or whose health has been undermined and resistance lowered by some chronic disease such as malaria, tuberculosis, scurvy or enteric. In the feeble-minded, in very young children, in the aged, and in pregnant women, bacillary dysentery is apt to assume a serious toxic aspect. Young children usually show pronounced symptoms of toxæmia, and die in convulsions or in coma.

Complications.—*Dysenteric arthritis*, or *dysenteric rheumatism*, has long been recognized in India. Effusions into the cavity and ligaments surrounding the joints, especially the knee and ankle, may take place during the acute stage, or, more generally, during convalescence when the stools are fæculent (Fig. 67). It may be common in some Shiga epidemics, absent in others. Considerable pyrexia is usually present. The condition may last a considerable time, but usually clears up without leaving deformity, though, exceptionally, permanent disability may result. According to Graham, complete recovery eventually ensues, even after arthritis has persisted for six months. Aspirated synovial fluid is sterile,[1] but agglutinates dysentery bacilli (Klein) in a titre considerably higher than that given by blood-serum. This condition has to be distinguished from fugitive serum-arthritis, such as sometimes occurs after injection of anti-dysenteric serum, and also from acute rheumatoid arthritis.

Eye complications.—Acute *conjunctivitis* and *iridocyclitis* are now regarded as symptomatic of dysenteric toxæmia. The former is frequently seen in association with arthritis, whilst iritis supervenes in a small percentage of cases. The pupils are irregular in outline, with ring synechiæ. There is also anterior uveitis, with adhesions to the capsule of the lens, formed by a thin exudate occupying the pupillary space, causing photophobia, blepharospasm and marked circumcorneal hyperæmia. The aqueous humour has been found to agglutinate Shiga's bacillus, though the tears do not contain specific agglutinins. That the eye and joint complications are due to the dysenteric toxin is indicated by experimental work on animals. This shows that the filtrates of Shiga cultures, when injected intravenously, produce iritis and arthritis, as well as local lesions in the cæcum.

---

[1] Shiga's bacillus has been isolated from the fluid in one instance (Elworthy).

Other complications.—Parotitis, unilateral or bilateral, has been often observed. Intussusception of the small intestine has been found in children, and in acute cases may cause death.

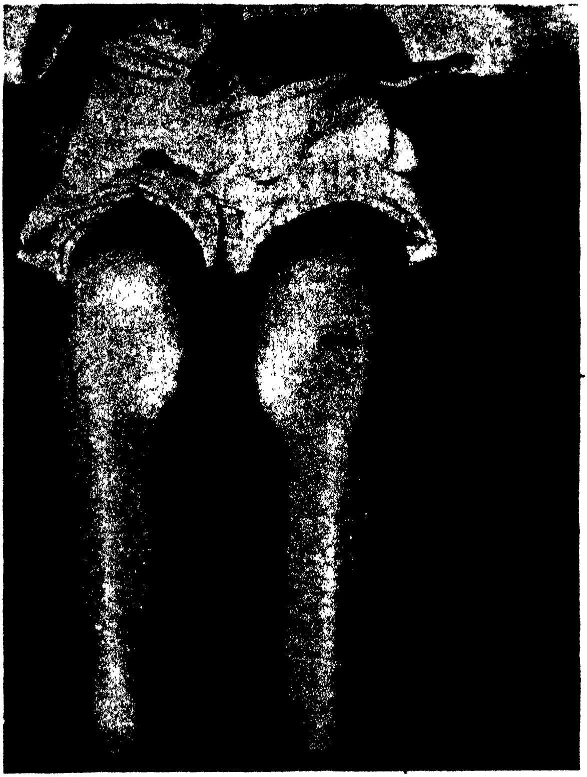


Fig. 67.—Arthritis of hands and knees in bacillary dysentery.

During the present war in the Middle East the list of complications has been amplified to include intestinal hæmorrhage, perforation with peritonitis, chronic peritonitis with localized or general effusion of peritoneal fluid, pneumoperitoneum, portal pyæmia with multiple liver abscesses, thrombosed piles, rectal prolapse, peripheral circulatory failure in toxic cases, renal failure in Shiga infections, pneumonia, and diffuse purpuric rashes. Non-specific urethritis is now also recognised.

Renal failure which has clinical resemblances to that found in traumatic anuria (crush injury) results from various factors, in which dehydration and toxæmia play a part, leading to reduced glomerular filtration and degenerative changes in the tubules. The urine contains granular casts and albumin, so that azotæmia and oliguria ensue, and may end in uræmia.

Sequelæ.—Stenosis of the large intestine may result from an acute attack. Pain and abdominal discomfort may indicate abdominal adhesions which are an occasional sequel. Rarely, megacolon may, apparently, be produced. Mucous colitis frequently persists for years. *Peripheral neuritis* of the legs may follow bacillary dysentery. *Post-dysenteric tachycardia*, or effort syndrome, a condition of irritable heart, may persist long after dysenteric symptoms have disappeared. *Achlorhydria*, rarely *achylia gastrica*, may be responsible for digestive troubles which may follow dysenteric infections.

Bacterium coli infections of the genito-urinary tract frequently complicate chronic bacillary dysentery as the result of the specific kidney lesions produced by dysenteric toxins. This possibly is the explanation of the comparative frequency of this infection in tropical residents.

Bacillary-dysentery carriers.—The " carrier question " in bacillary dysentery is probably not so serious as in typhoid, as the bacilli remain confined to the intestines and to the mesenteric glands.

There are many circumstances which render the " carrier state " in bacillary dysentery difficult to detect. Dysentery bacilli, as a rule, are scarce and likely to escape detection in a fæcal stool, though with improved methods of isolation by desoxycholate agar, the carrier rate has been found to be about 10 per cent. It is probable that carriers are the starting-point of an epidemic. The majority are " *convalescent carriers*," a term which implies that the patients have incompletely recovered, and continue to pass blood and mucus and dysentery bacilli in their stools. There is no evidence that the gall-bladder acts as a reservoir, as in typhoid ; or that the " carrier state " persists for any great length of time. The organisms continue to live in mucous retention cysts in the intestinal mucosa, in collections of pus from beneath the scars of ulcers or beneath their edges. The maximum period that this carrier state can last is about three years.

Carriers of Flexner bacilli are much commoner than those of Shiga. Generally, the Flexner carrier is in good health, while the Shiga carrier is more or less an invalid.

Sometimes bacillary inflammation or ulceration is localized to the lower rectum (granular rectitis). These patients pass blood and mucus in their stools, though otherwise in good health. The bacillus may be isolated, by means of rectal swabs, a year or more after the initial attack. Fortunately they are easily cured by sulphaguanidine (*see* p. 482).

Microscopic examination of the fæces usually affords little assistance in these cases. The chances of isolating the specific bacillus are considerably increased by making cultures direct from the mucosa by rectal swabs, or from scrapings of ulcers obtained through the sigmoidoscope.

Dysentery bacteriophage.—D'Herelle observed that filtrates of convalescent dysentery stools developed the property of clearing broth cultures of Shiga's bacillus, but when a few drops of filtrate were added to a fresh culture, the bacilli were again dissolved, and that this process could be repeated indefinitely. Shiga's bacillus was first recognized as susceptible to bacteriophagy. The bacteriophage consists of ultra-microscopic particles measuring 20–30 mμ. Many races of bacteriophage are virulent for Shiga's bacillus, but that obtained from Flexner bacilli is active solely for the homologous organisms. Bacteriophage has been isolated from the stools of patients convalescent from acute and mild bacillary dysentery. It appears probable that improvement in the clinical condition coincides with the increased bacteriophagic potency. Dysentery bacteriophages have been prepared for therapeutic use.

Diagnosis.—Difficulty in the diagnosis of bacillary dysentery on clinical grounds is mainly confined to the milder forms. Whenever possible, a confirmatory laboratory diagnosis should be carried out.

The possibility of malaria in the course of bacillary dysentery should always be borne in mind. The concurrence of a subtertian malaria with bacillary dysentery may be particularly serious.

A tentative diagnosis may be made from a microscopic examination of the *cellular exudate* in the stools by the method known as cyto-diagnosis. For this purpose the specimen should be procured fresh from the patient and as early as is possible in the disease. The characteristic feature of the bacillary stool (Plate XI), is the preponderance of swollen *polymorphonuclear leucocytes*, with distinctive ring-like nuclei, which constitute over 90 per cent. of the total cell elements in the stool. The examination should be conducted with a ⅙-in. lens and a low ocular (× 2).

Macrophage cells (*histiocytes*).—These cells, sometimes 20–30 μ in diameter, are derived from the endothelium of the capillary vessels. They may be round, oval, or even bilobed. They are hyaline, and contain in their substance vacuoles, fatty granules, ingested red blood-corpuscles, or even, occasionally, leucocytes. They are non-motile, but, owing to their phagocytic activities, are apt to be mistaken for *Entamœba histolytica*.

The differential-cell picture in dysenteric exudates has been distinguished by Alexeieff as a " pyogram." In amœbic dysentery fæces the cellular elements are few and mononucleated ; in bacillary dysentery, numerous and polymorphonuclear, with *pseudopyknotic nuclei*.

It is important that the significance of macrophage cells in bacillary dysentery stools should be emphasized. Willingness to diagnose amœbic dysentery is very pronounced in almost every tropical country. It is most important that pathologists should acquaint themselves with the appearance of inflammatory cells in the fæces, as well as with the different stages of the dysentery amœba, before an expert diagnosis is given. The main features of the cyto-diagnosis of dysentery stools were pointed out by the Editor in 1912 and this method was practised throughout the 1914–1918 war, since when, especially in recent epidemics, its value has been amply confirmed.

Entamœba coli and flagellate protozoa (*Chilomastix* and *Trichomonas*) may be seen in considerable numbers in a bacillary-dysentery exudate, especially during the convalescent stages. Some difficulty may be experienced in differentiating *E. coli* from *E. histolytica* in bacillary-dysentery stools.

Isolation of the dysentery bacillus.—The stool should be collected in a bed-pan, *which should contain no disinfectant*, and the patient should be warned against passing urine. A portion of freshly-passed blood and mucus should be picked out by a platinum loop, and, if soiled with fæces or urine, should be rinsed in 5 c.c. of distilled water or normal saline solution. The earlier in the illness, the easier it is to isolate the dysentery bacillus. It is, as a general rule, difficult when the dysentery has lasted five days or longer. Fæces despatched for laboratory examination through the post, or by messenger over long distances, should be emulsified with a double volume of buffered glycerol saline—1 part of glycerine to 2 parts of saline, buffered by the addition of 5 per cent. acid sodi phosph., at pH8. The mixture is tinted with phenol red so that any change in acidity can be detected. Dysentery bacilli are very delicate, and never occur in great numbers, even in a freshly-passed stool. The mucus, or two loopfuls of the suspension, should be spread, in a spiral manner, somewhat thickly, upon a MacConkey agar plate, or, better, on desoxycholate citrate agar, which inhibits to some extent the growth of *Bact. coli*. The plate should be incubated at 37° C. in an inverted position for eighteen hours, when the small blue transparent colonies can be examined with a watchmaker's lens. As a rule, Shiga colonies are more refractile and of a more regular outline than are those of the Flexner-Y group. It is a good plan to hold a piece of dark paper against the back of the plate to make their recognition easier.

Identification of the colonies may be carried out as follows: four or more should be picked off with a platinum spud and transplanted on to agar slopes, and, after further incubation, these subcultures should be emulsified and tested in high dilutions against Shiga and Flexner sera in agglutination tubes. The macroscopic method is usually employed, or the test may be performed on a microscope slide or on the agglutinometer. By means of a capillary pipette, drops of bacillary emulsion are placed together with an equal quantity of specific sera diluted to 1 in 50. The resulting dilution will then be 1 in 100. After oscillation for three minutes, should the reaction be positive, snowflake agglutination occurs.

After these measures, diagnosis may be confirmed by inoculating subcultures of the organism into the sugars (Table VII, p. 468). Direct culture by the rectal swab method offers obvious advantages and results in a higher proportion of positives.

Isolation of the dysentery bacillus post mortem.—The bacillus can be isolated from the acutely inflamed mucosa by washing the canal free from intestinal contents and scraping off the blood and mucus with a platinum loop, but from necrotic mucosa this is by no means easy. In this case the surface must be first seared with a hot knife or glass and incised, and material for culture obtained with a platinum loop from the bottom of the incision.

Serological diagnosis.—This is of little value as an aid in the early stages of the disease, or in the very acute or rapidly fatal types in which it is so important to arrive at an accurate diagnosis. The sera of some patients, proved to be suffering from bacillary dysentery by isolation of the specific organisms from the stools, may give negative agglutination reactions.

For the diagnosis of Shiga infections in convalescent or chronic cases, positive agglutination of over 1 in 25 should be obtained. In Flexner infections an agglutination of 1 in 100 indicates positive diagnosis. Davies found dysenteric agglutinins were present in dysenteric stools, even when absent from the serum of the patient, especially during the first week. Blood and mucus from the fresh exudate are shaken up with normal saline, filtered and put up for agglutination in the same way as serum.

Serological diagnosis may be of considerable assistance in chronic bacillary dysentery, where high-titre agglutinations are sometimes obtained, especially with emulsions of the pooled Boyd strains of Flexner bacilli.

Serological diagnosis of Sonne dysentery by the agglutination test is also somewhat unreliable, and appears to depend, to some extent, on the strain of organism employed as antigen.

An intracutaneous test for Shiga dysentery, with Shiga toxin, was introduced by Brokman (1923). A negative reaction is diagnostic of infection. Dreyfuss (1944) used a Flexner vaccine (5 million bacilli), which gives a cutaneous reaction in positive cases.

Sigmoidoscope examination.—Sigmoidoscopy reveals pathological changes in the colon and therefore plays an important part in the differential diagnosis of the dysenteries. It is especially useful in chronic cases, and should be employed wherever practicable. For preparation of the patient, a cathartic of ½ oz. of castor oil is given : the following morning the bowel is cleared out by a warm-water enema. If the patient has acute diarrhœa, omission of castor oil is advisable, though in any case it should not be given later than 2 p.m. on the day preceding examination. It is advisable to give 10–15 min. of tincture of opium half an hour before in order to render the rectum less sensitive. The mucous membrane of the rectum is replaced by granulation tissue with surrounding hyperæmia, and has a characteristic appearance resembling the cortex of a granular kidney ; at the same time infiltration of the bowel can be detected (Plate XIII). Superficial oval or circular ulcers, up to 1 cm. in diameter, are also seen in the chronic stage, and sometimes even pseudopolyposis of granulation tissue. In the healing stage the mucous membrane is rose-pink and slightly nodular. Widespread superficial pitting at the site of former ulceration is characteristic and it is possible by this feature to state definitely that the patient had suffered from bacillary dysentery. The passage of the instrument is attended by pain due to stretching of the bowel wall. This is almost diagnostic, as in amœbic ulceration it is usually painless.

Differential diagnosis of the dysenteries will be dealt with on p. 525.

Prognosis depends very much upon individual susceptibility and physical condition. In the jails of India, in fact throughout that country, though bacillary dysentery is widespread, the case-mortality is very small. In many thousands of cases among British troops in the 1914–18 war, it is doubtful whether it at any period rose above 5 per cent. Epidemics in native races have been recorded where the mortality was over 28 per cent., and others among debilitated Solomon Islanders in which it was 47 per cent. Prognosis is unfavourable in chronic cases, especially in poverty-stricken, malaria-infected, half-starved natives.

Treatment.—The patient should be placed in bed on the appearance of the first signs, and should on no account be permitted to get up in order to pass his motions. A bed-pan should therefore be employed wherever nursing facilities are available. In the choleraic or fulminating cases in which the passage of stools is incessant, and the physical exhaustion consequently very great, it may be advisable to dispense with a bed-pan altogether. The patient should then be placed upon a waterproof sheet with a gamgee dysentery pad. For this purpose the attendant, for self-protection, should wear rubber gloves, as the discharges are highly infectious.

The stools should be periodically inspected, for by these, supplemented

Fig. 1. Acute bacillary dysentery (Shiga infection). Note œdema of mucosa and submucosal hæmorrhages.

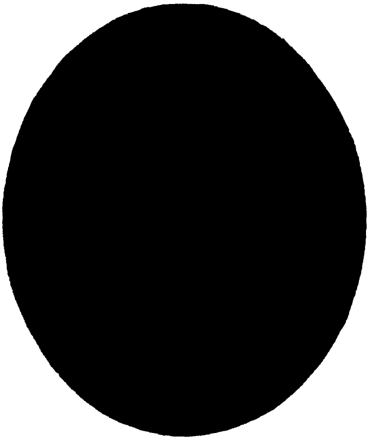


Fig. 2. Chronic bacillary dysentery (Flexner infection). Note granulations on mucous membrane.

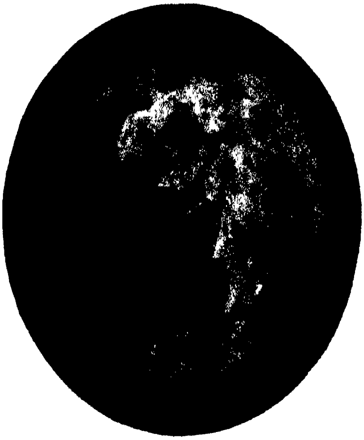


Fig. 3. Acute amœbic dysentery. Note folding of lax mucous membrane, pin-point ulcers and surrounding submucous hæmorrhages.

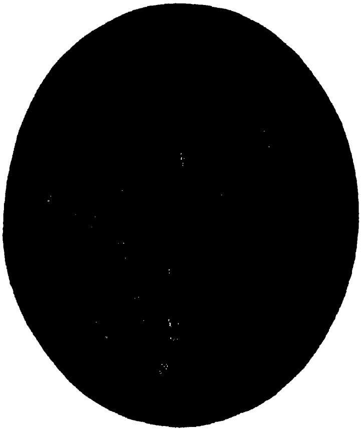


Fig. 4. Chronic amœbic dysentery. Note diamond-shaped ulcers and submucous hæmorrhages.

SIGMOIDOSCOPIC APPEARANCES OF RECTUM IN BACILLARY AND AMŒBIC DYSENTERIES.

PLATE XIII

TABLE VIII

Diagnosis between Bacillary and Amœbic Dysentery

BACILLARY DYSENTERIES	AMŒBIC DYSENTERY
Acute diseases with a tendency to epidemic spread. "Lying down dysentery."	A chronic endemic disease. "Walking dysentery."
Incubation period short, 7 days	Incubation period long, at least 20–90 days; it may be more.
Onset acute.	Onset insidious.
Pyrexia common.	Pyrexia rare, unless complicated.
Course days or weeks.	Course usually prolonged for years.
Complications: Polyarthritis frequent; eye complications.	*Complications:* Hepatitis, abscess of liver; abscesses more rarely in other situations. Pericolic abscess. Amœbic infection of skin.
Death due to— (*a*) Exhaustion. (*b*) Toxæmia. (*c*) Glomerulonephritis.	Death due to— (*a*) Exhaustion. (*b*) Perforation. (*c*) Hæmorrhage. (*d*) Liver abscess.
Signs: Tenderness over whole abdomen, more marked over sigmoid flexure.	*Signs:* Local tenderness and thickening, mostly over sigmoid flexure, transverse colon, and cæcum.
Tenesmus very severe.	Tenesmus not usually noted.
Pathology: Acute diffuse necrosis of mucous membrane of large intestine, due to dysenteric toxins.	*Pathology:* Local lesions confined solely to the large intestine, due to the characteristic ulcers.
Ulcers: When present, on free edge of transverse folds of mucous membrane and distributed transversely to long axis of gut.	*Ulcers:* Commence as small abscesses of submucosa in long axis of gut. "Flask-shaped ulcer," or *Bouton en chemise*, "sea anemone" ulcers.
Serpiginous in outline, with ragged undermined edges, often communicating with neighbouring ulcers; bases consist of granulation tissue.	Oval, regular, flask-shape in section, involving all coats; bases consist of necrotic black tenacious sloughs ("Dyak-hair" sloughs).
Intervening mucous membrane hyperæmic. Ulcers rarely perforate. No compensatory thickening of bowel-wall.	Not uncommonly perforate; compensatory thickening of bowel-wall. Intervening mucous membrane normal.
Stools: Scanty; many in number. Bright blood-red, gelatinous, viscid mucus, odourless, resembling red-currant jelly.	*Stools:* Fæces intermingled with blood and mucus, resembling anchovy sauce (sago-grain stool). Offensive, smelling of decomposing blood; generally copious.
Reaction: Alkaline.	*Reaction:* Acid.
Microscopic picture: Numerous red cells; polymorphonuclears numerous, with clear-cut ring nuclei, Macrophage cells. Few micro-organisms visible (Plate XI).	*Microscopic picture:* Red cells numerous and in clumps, polymorphonuclears damaged, often extruded nuclei. Macrophage cells scanty. Large numbers of motile bacilli and ***Entamœba histolytica***, generally with ingested red cells. Charcot-Leyden crystals common (Plate XII).
Blood examination: Leucocytosis in the early stages.	***Blood examination:*** Usually a moderate leucocytosis throughout.

by the appearance of the tongue and the general condition of the patient, the progress of the case can best be ascertained.

Attention should be paid to the diet, which should be nutritious and easily assimilable, leaving as little residue as possible. Nothing but water should be given for the first twenty-four hours. The best diet is one consisting of tea, jellies, albumin water, rice water, chicken soup, beef tea, Brand's essence, arrowroot, Horlick's, Bengers, sago puddings, any of which may be given at two-hourly intervals in small quantities (6–10 oz.), slightly warmed, at each feed. Non-residue diet should be instituted when blood and mucus have disappeared from the stools. Treatment should be preceded by a mild purge, the most suitable being sodium or magnesium sulphate. The routine treatment with saline aperients was once almost universally employed, but is not now recommended, especially in dehydrated cases.

Sulphaguanidine (p-amino-N-guanylbenzene sulphonamide) is a guanidine analogue of sulphapyridine. It was first prepared by Buttle and colleagues, though Marshall and others described its chemical constitution. It exerts a bacteriostatic effect on various bacteria *in vivo* and *vitro*. It is moderately soluble in water, insoluble in strong alkali.

High concentration can be obtained in the intestine associated with low concentration in the blood (2–5 mgm. per 100 c.c.) and tissues. Urinary excretion is three times as rapid as that of other sulphonamides. Although sulphaguanidine may be excreted as crystals, no renal complications have so far been reported. The drug is undoubtedly less toxic than other sulphonamides. The toxic reactions observed include headache, malaise, purpuric skin rashes, mild pyrexia and anæmia. Agranulocytosis or jaundice have never been observed.

The dosage of sulphaguanidine in acute bacillary dysentery is: an initial dose of 0·1 grm. per kilo (or 9½ gr. to the stone (14 lbs.) body weight), a maintenance dose of 0·05 grm. per kilo four-hourly for the period during which the number of stools exceeds five per day, and a further maintenance dose of 0·05 grm. per kilo every eight hours until the stools have been normal in number and consistency for two days. Duration of treatment should not exceed fourteen days. If necessary, the course may be repeated. In chronic bacillary dysentery larger doses are necessary: 0·1 grm. per kilo every eight hours for the first five days, followed by a dosage of 0·05 grm. every eight hours for another five days; this may be repeated in fourteen days. The total dosage in acute cases varies from 18 to 350 grm.; the average effective dose in acute cases is about 130 grm., sometimes between 100 and 200 grm. In less acute cases the dose should be 18 grm. in the first twenty-four hours, administered in 6 grm. doses three times daily and subsequently 3 grm. three times daily for five days.

The effects may be judged by the change in the patient's general condition and the improvement in the stools which, in most cases, become porridgy and fæcal in forty-eight hours. A diminution in temperature, pain and toxæmia take place within twenty-four hours. The mortality rate, in the very extensive series so far reported upon from the Middle East is less than 1 per cent. Succinyl sulphathiazole (sulphasuccidine) appears to be equally effective, according to Poth and colleagues, especially for children. Sulphapyridine and sulphamethazine in maximal doses are also curative, but are more depressing and much more toxic. According to Fairley and Boyd, sulphaguanidine treatment should be combined with preliminary dosage with magnesium and sodium sulphate and, after two hours, with gentle colonic lavage with one pint of normal saline.

The indications for sulphaguanidine treatment are : cases of proven Shiga dysentery, or other infections with dysentery bacilli with frequent dysenteric stools, toxæmia and dehydration ; cases with collapse, profuse vomiting and choleraic stools ; all cases over 40 years of age, and those who develop acute bacillary dysentery in the course of some other illness. Very large doses of sulphasuccidine can be given with safety, and it is apparently even more effective than sulphaguanidine.

Opium.—Either by the injection of morphia or in solution, opium is indicated as a means of promoting sleep and relieving pain, if very severe.

Bolus alba (*kaolin*).—As a means of checking the diarrhœa and of eliminating the dysentery toxins in the intestinal canal, a mixture of animal charcoal and kaolin has been utilized in Germany and in Austria ; the powder should be given suspended in water in doses of three teaspoonsful every few hours. Crooke's collosol kaolin has much the same effect.

Anti-dysenteric serum.—Since the introduction of sulphaguanidine the value of antidysenteric serum has been discounted. It is now employed principally in toxic Shiga cases. Refined anti-Shiga serum, prepared by the Pope process of partial peptonization containing 20,000 International Units per c.c., is given intravenously in doses of 5 to 10 c.c. and may be repeated daily. The anti-toxic effects appear to be transient. It is best combined with sulphaguanidine therapy. No serum reactions have been observed with this new preparation.

Bacteriophage treatment.—Recovery from an acute attack of bacillary dysentery is connected with production of a corresponding amount of bacteriophage in the intestinal canal. A potent anti-Shiga phage has been prepared by d'Herelle, Morison, and others, but it is particularly difficult to obtain accurate statistics on the efficacy of this treatment. This phage is distributed in ampoules in quantities of 2 c.c. The patient takes three ampoules by the mouth daily, or it may also be injected *per rectum*. Whenever this method has been subjected to critical analysis, as in the Middle East during the present war, the results have not been conclusive, although it appears to have acquired a reputation in Egypt.

Relief of pain.—During the early stages of an attack the patient may suffer much from griping and tenesmus. These are generally relieved by a hot bath, hot fomentations, or turpentine stupes, three or four of which may be sewn into a piece of flannel and laid on the abdomen. This application has the advantage of being very light, of not wetting the clothes, and of keeping warm for many hours. Tenesmus and dysuria are best relieved by hypodermic morphia ; by an enema of a wineglassful of thin starch containing 40 or 50 drops of tincture of opium ; or by suppositories of morphia and cocaine. Washing out the lower bowel with a pint of hot water, with or without boric acid, is sometimes effectual in removing for a time, or, at all events, mitigating, the incessant desire to go to stool and to strain. Bismuth carbonate, 2 dr., with tincture of opium, 30 min., and thin starch, 2 oz., is also a good sedative enema. Painful colic or peristaltic action may be counteracted by the following mixture :

℞ Tinct. belladonnæ	♏vii	(0·414 c.c.)
Pot. brom.	gr.x.	(0·648 grm.)
Tinct. chlor. et morph. co.	♏x	(0·592 c.c.)
Syrup. aurant.	ʒi	(3·55 c.c.)
Aq. menth. pip. ad	℥ss	(14·2 c.c.)

Ft. mist. ℥ss t.d.s., p.c., vel p.r.n.

Collapse from dehydration and vascular failure may occur at almost any stage. An attempt should be made to restore the balance by the intravenous injection of large quantities of saline and glucose. Blood and plasma transfusions have been employed in these cases with striking benefit during the present war.

Vomiting and hiccough in severe cases should both be regarded as serious.

Treatment of complications.—*Arthritis* is best treated by application of Scott's dressing, radiant heat, or sand-baths at 45°–60° C.

Sulphaguanidine treatment appears to be specially efficacious.

When the joint is greatly distended the excessive fluid may be aspirated. *Iritis* is treated by atropine, the use of an eye-shade and the usual measures.

The treatment of chronic bacillary dysentery has been radically altered since the introduction of sulphaguanidine, which should be given in full doses over a prolonged period of fourteen days or longer. Fairley and Boyd, by periodic sigmoidoscopic examination, observed healing of chronic ulcers, and even those with exuberant granulations and pseudo-polyposis appear to do well, but it is often necessary to repeat the course of sulphaguanidine. In refractory cases it may be necessary to inject the sulphonamide by retention enemata, in doses of 7–10 grm. daily, suspended in water and mucilage (7–10 ounces). This medicated enema is retained from three to four hours.

Moro's apple dietary has been used extensively in chronic dysentery in Germany, both for adults and children ; twenty or more apples made into a purée are eaten daily. A preserved apple powder, *Aplona*,[1] is made in Switzerland. In grave cases nothing besides Aplona is given for three days. The dose for adults is 1–1½ oz. (3½ oz. of Aplona = 360 calories), and the amount required for a day is divided into portions, each of which must be freshly prepared with boiled water at drinking temperature, or with weak tea, 60–120 gr. to ¼ pint of liquid. It must not be brought to boiling point and no sugar should be added, but saccharine may be substituted. After the third day it may be added to gruel or milk, being first mixed as a smooth paste with water.

Surgical treatment of chronic bacillary dysentery.—When less heroic methods fail, and the patient's condition is slowly but progressively deteriorating, right inguinal colostomy offers a reasonable chance of success. More usually, *appendicostomy* is performed. The cæcum and colon may now be washed out with normal saline, or with an astringent solution, such as tannic acid (2 per cent. solution), through the appendix, as frequently as desired. For this purpose a No. 8 rubber catheter with a copper stylet, and rectal tube with an outflow tube are used. The patient should lie on his back ; but should the cæcum get distended and the fluid fail to pass freely, turning on the left side will restore the flow.

---

[1] Sold by Coates and Cooper, 94 Clerkenwell Road, London, E.C.1.

Cæcostomy and ileostomy.—In cases with pseudopolyposis of the mucous membrane and incessant distressing blood-stained diarrhœa, the operation of valvular cæcostomy should certainly be given a trial. The results have been successful in some cases which were incurable by other means. A Paul's tube is first inserted into the cæcum and the fæces are allowed to escape through it, thereby placing the whole of the large intestine at rest. Then an efficient opening is made. The lower bowel may be washed out daily with boric acid solution, and the opening may be closed at some subsequent period, after the large bowel has been permitted to rest for three months or more ; complete recovery of the mucous membrane has been observed by sigmoidoscopic examination. A colostomy bag is fitted. The patient may be sent to convalesce and encouraged to consume plenty of fresh eggs, milk and fruit. One-barrelled ileostomy is sometimes preferable and is recommended by some surgeons. The indications here are the same as in ulcerative colitis, but it condemns the patient to a permanent colostomy belt and other disagreeable sequelæ.

Ispaghula.—The boat-shaped seeds of *Plantago ovata* have acquired a popular reputation in the treatment of chronic dysentery in India. The seeds are either chewed, when a gelatinous substance exudes which acts as a demulcent, or the pericarp is made into a paste. If taken in 1-dr. doses three times daily, it has a soothing effect. Singh recommends a fresh decoction prepared daily by boiling two drachms of the seeds in one pint of water, and subsequently straining. Chopra has shown that these seeds contain a glucoside *aucubin.* The mucilage which exudes from the seeds is acted upon by the digestive enzymes and coats the inflamed mucosa.

Prophylaxis.—The prophylaxis of bacillary dysentery consists principally in securing a pure water supply and in avoiding unwholesome and contaminated food ; also in eliminating flies from latrines and in protecting food against them. In barracks, camps, lunatic asylums, and other public institutions, bacillary dysentery should be regarded as an infectious and readily communicable disease, and therefore patients suffering from mild symptoms, or even looseness of the bowels, should be isolated.

To prevent the spread of bacillary dysentery in closely crowded communities, it is important to recognize, as early as possible, all carriers and mild cases which might otherwise escape recognition. Cunningham and others have pointed out that, in the prevention of the spread of bacillary dysentery in jails, it is essential that the stools of the inmates should be inspected daily. Any inmate found passing blood and mucus, even in small quantities, should be regarded as potentially infectious and as possibly constituting a carrier of the disease.

The treatment of carriers.—The chronic carrier has in the past been difficult to treat effectively, but sulphaguanidine has transformed the situation. It is recommended that this drug should be given in maximal doses for periods of 5–7 days, though it is usually necessary to repeat the course. For the drug to exert its maximum action, the fæces must be kept as fluid as possible by means of sodium or magnesium sulphate. Carriers of Sonne's bacillus appear to be especially difficult to cure.

Prophylactic inoculations.—The Japanese workers, and later Gibson in England, introduced an inoculation by which the toxic effects of the bacillus are neutralized by a potent anti-Shiga serum, resulting in an almost complete absence of reaction. The vaccine and serum (sero-vaccine) are enclosed in twin phials, the bacillary emulsion being contained in one arm, the serum in the other. The first dose was 0·25 c.c., containing 500 million Shiga organisms mixed with 0·1 c.c. of serum ; the second dose, given 10 days later, contained 1,000 million organisms with 0·2 c.c. of serum.

The results were distinctly in favour of this method of protection.

A similar preparation was used in Germany and in Austria as "*Boehncke's Dysbakta.*" Besredka produced an antidysenteric bilivaccine consisting of dead dysentery bacilli with the addition of bile. The technique is to give on three successive days before breakfast a dose of bile, followed by a pill containing the desiccated vaccine.

Blanc and Caminopetros employed intramuscular injections of *living vaccines* consisting of 4–6 thousand million dysentery bacilli, and found that they caused slight reactions which resolved three or four days later. They concluded that there is no particular danger in using living vaccines.

Trials are being made with preparations containing dysenteric endo- and exotoxins, and also phenol-extracts of the O antigen of *B. Shigæ* ; this latter excites the appearance of specific agglutinins in the serum after inoculation (Morgan and Schutze).

II. AMŒBIC DYSENTERY AND AMŒBIASIS

Definition.—Amœbiasis denotes infection with the protozoon, *Entamœba histolytica.* When confined to the intestinal canal it produces *amœbic dysentery,* or primary intestinal amœbiasis. This is insidious in its onset, chronic in its course, and with a marked tendency to relapse. When metatastic lesions are produced in the liver and elsewhere it should be known as secondary, or *hepatic amœbiasis.*

Geographical distribution.—Amœbiasis occurs to a greater or lesser degree throughout the tropics and subtropics. During recent years sporadic indigenous cases have been found in Northern Europe (Russia, Norway and Germany) and even, rarely, in Great Britain. Specially prevalent in India, Indo-China, China, and the Philippines, it is common throughout North and Central Africa, widespread in the Southern United States, South America, and the West Indies.

Epidemiology and endemiology.—A disease of insanitation, not necessarily requiring tropical or subtropical conditions for its propagation, amœbiasis arises sporadically without seasonal prevalence, but does not usually occur in epidemic form in the same manner as the bacillary dysenteries. Wenyon and O'Connor have shown that the cysts of *E. histolytica* can be demonstrated in the fæces of house-flies sixteen hours after ingestion, and that flies play a part in the dissemination of amœbiasis. There is also much evidence that *contaminated water* and even fresh vegetables, such as lettuce, may constitute sources of infection.

Reports of the outbreak in Chicago in the summer and autumn of 1933 gave the total number of cases as 1,409, in that city or traced to other cities in the United States, with over 40 deaths. The source was traced to two hotels, where the majority of those infected were servants or guests. All carriers of *E. histolytica* were removed from employment, but in spite of these measures, cases continued to develop amongst employees of one hotel, where the " carrier " rate was found to be as high as 47·4 per cent. Further investigations revealed serious contamination of the water supply from defective drainage and that drinking water formed the main channel of infection.

Considering the susceptibility of the cysts to desiccation, it is probable that dust and sand play no part in dissemination.

Intestinal amœbiasis is a disease of adult life as a rule. It is rare in European children under five years of age, but among Egyptians of the poorer class in Cairo, Perry and Bensted found that 13 per cent. of clinical dysentery was due to *E. histolytica*. Biggam diagnosed acute amœbic dysentery with liver abscess in an infant three months old, and Williams found it in a negro infant of fifteen months on the Gold Coast. As the disease has a long incubation period and is acquired from contaminated water and vegetables, it is unlikely to occur among carefully nurtured children, in whom the bacillary form is much more common.

Intestinal amœbiasis may produce active symptoms for many years. The Editor has treated infections which have persisted from thirty to forty years without seriously undermining the patient's health, so tolerant are the tissues to *E. histolytica*. There appears also to be a difference in incidence of intestinal amœbiasis in the sexes. Males, European and native, are more apt to contract the infection. Gharpure and Saldanha (1930) reported that in a series of over 400 post-mortem examinations the number of male cases was quite disproportional to the total. Of amœbic dysentery and liver abscess, 90·3 and 93·8 per cent. respectively occurred in males ; 9·4 and 6·2 per cent. in females. Below ten years of age the incidence of amœbic lesions was 0·9 per cent. and of liver abscess nil. The highest peak is reached in the decennial periods 20–40, with a proportion of about 30 per cent. of amœbic dysentery and 38 per cent. of liver abscess to the total number of autopsies.

In Armenia, Zaturjan showed that amœbiasis in children usually runs a much more benign course than in adults and rarely shows any serious complications.

Ætiology.—The discovery of amœbæ in dysentery stools was made by Lösch in 1875. Originally regarded as a single organism—*Amœba coli*—it is now recognized, mainly as a result of the work of Schaudinn, Hartmann, Wenyon, and Dobell, that several distinct species occur in the intestinal canal of man, one of which, *Entamœba histolytica*, is pathogenic for man, while others—*Entamœba coli, Endolimax nana, Iodamœba bütschlii* and *Dientamœba fragilis*—are harmless species. *E. histolytica* was originally cultured on egg-medium by Boeck and Drbohlav in 1925 (p. 1018), but during the last few years it has been grown on a variety of serum-media. The term *Entamœba* is employed by English authorities, though American writers claim that *Endamœba* is more correct.

Detection of Entamœba histolytica in stools.—When present in stools, entamœbæ are generally easy to find. It is necessary to pick out a small fragment of stool shortly after it is passed, and to lay it on the slide and compress it under the cover-glass to form a fairly transparent film. Active entamœbæ tend to occur in clumps or masses and are not evenly distributed throughout the stool; they may be present in one evacuation but not in the next. Care should be taken that the receptacle in which the stool is collected is free from all traces of antiseptic. These amœbæ live in the fæces for a few hours after being passed and are readily distorted in the presence of urine. The dysentery amœba is a clear, faintly greenish-tinted, transparent body, as a general rule, some three to five times the diameter of a red blood-corpuscle. In its vegetative or tissue-invading phase it is recognizable by its active movements, as well as by the presence of extraneous material, such as red blood-corpuscles, which it ingests. The nucleus may sometimes be excentric. The habit of ingesting red blood-corpuscles and body-tissue cells is one of the points of distinction between *E. histolytica* and non-pathogenic *E. coli*.

In fresh and in stained preparations[1] the amœba is seen to be made up of two zones—a granular endoplasm surrounded by a clear protoplasmic ectoplasm. The nucleus shows a characteristic uniform structure if the specimen is fresh and fixed while alive; aberrant forms with fragmented karyosomes, etc., are due to degenerative changes (*see* p. 865).

These amœbæ flow, rather than move, across the slide, and in the living state do not always exhibit conspicuous differentiation between ectoplasm and endoplasm. They quickly die and degenerate outside the body. At lower temperatures they remain stationary, but when the slide is warmed, they eject from time to time hyaline "blade-like" pseudopodia (Fig. 68). Degenerating entamœbæ often contain vacuoles, but these are not normally present. When conditions become adverse, they encyst, first passing through a precystic stage.

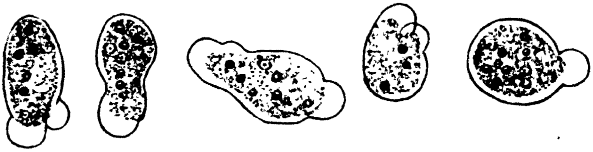


Fig. 68. Camera lucida drawings showing protrusion of pseudopodia by *Entamœba histolytica*. (*P.H.M.-B. del*)

Cysts.—Cysts vary much in size. They contain highly refractile masses of chromatin or chromatoid bodies, which may assume the form of blocks with rounded ends, and also glycogen-containing vacuoles. When first formed, the cyst contains one nucleus, which measures about one-third of its diameter. This divides by binary fission, so that finally, in the more mature individuals, four small nuclei, each measuring one-sixth of the diameter of the cyst, are produced. In general characters the nucleus of the cyst resembles that of the vegetative stage.

Cysts of *E. histolytica* can survive outside the body of man for about ten days if kept moist and cool. Desiccation kills them immediately, though they survive much longer at lower than at higher temperatures.

Westphal has recorded a significant experiment where an apparently harmless *E. histolytica* infection was acquired by the ingestion of cysts. Some months later cultures of bacteria isolated from the fæces of acute amœbic dysentery were ingested and a similar dose was given to a control. Both the "carrier" of *E. histolytica* and the control suffered from diarrhœa, but on the twenty-third day, the former developed clinical amœbic dysentery. It was finally determined that super infection with Flexner bacilli excited the clinical manifestations of amœbic dysentery. Some workers therefore believe that symbiotic bacilli aid, or in some way instigate attacks of acute amœbic dysentery.

---

[1] For the staining of amœbæ in liquid preparations, *see* Schaudinn's method (Appendix, p. 1012). The details of amœbæ are distorted if attempts are made to dry the specimen as in a blood-film.

Summary of life-history of Entamœba histolytica.—The active vegetative entamœbæ live on the tissues of the gut-wall, where they ingest blood-corpuscles and multiply by mitosis. In primary amœbic lesions they make their way into the follicles of the large intestine, where they multiply and, partly by pressure, partly by cytolysins, dissolve the interglandular tissues, producing small amœbic abscesses in the submucosa which burst and become ulcers. A number of amœbæ enter the lumen of the bowel, encyst, and pass out with the fæces. The precystic individuals, which are free from protoplasmic inclusions, congregate on the surface of the bowel. They are smaller than the vegetative forms which continue to multiply in the tissues. Typical cysts, smaller than precystic forms, are quadrinucleate when fully mature. When swallowed by another host they pass into the small intestine, where they hatch into amœbulæ which attack and invade the tissues. (*See* Appendix, p. 866).

This summary epitomizes the generally accepted account of the life-history of *E. histolytica*, but there are some observers, notably Reichenow, who consider that it is normally an inhabitant of the lumen of the intestinal tract and not a tissue-invader, but that, under certain conditions, the amœbæ may invade the intestinal wall and thereby give rise to clinical amœbic dysentery. He thinks that the normal form is the *minuta* form, which lives in the intestinal lumen, where it reproduces by binary fission and produces four-nucleated cysts. Westphal, on the other hand, regards *E. histolytica* as capable of both intra- and extra-cellular digestion. Proteolytic ferments, not toxins, are produced. Colonization is in the tissues.

A characteristic feature of amœbic infection of the intestine is the periodic variation in intensity, which may be connected with resistance on the part of the tissues of the host, or possibly constitutes a feature in the developmental cycle of the parasite.

Occasionally, however, vegetative amœbæ migrate from their site in the bowel-wall and, as tissue-invading forms, enter the venous system and are transported to the liver, exceptionally to the spleen, brain or lung; but by so doing they become unable to complete the cycle of development as observed in the intestine, for pre-cystic individuals and cysts never develop in these situations. Amœbic infection of the skin has been seen quite often (*see* p. 521).

E. histolytica passers.[1]—The healthy passer (or excretor) of *E. histolytica* is an individual who has not suffered, and is not suffering, from dysenteric symptoms, but passes *histolytica* cysts, though otherwise in good health. Such cyst-passers may have active entamœbæ in the tissues of the bowel.

The cyst-passers may be divided into two classes—(1) *contacts* who have never suffered from clinical amœbic dysentery, and (2) *convalescents* who have recovered from an attack. It is known that, for every abnormal person who is suffering from amœbic dysentery with passage of vegetative forms which are non-infective to other individuals, there are large numbers of healthy persons who continue to pass *E. histolytica* cysts, thus constituting a perennial source of infection. The vegetative entamœba must, in either case, exist on the tissues of the host. We know from post-mortem findings in the Philippines, New Orleans and elsewhere that ulceration can occur without producing signs or symptoms, and it is well known that liver abscess may be produced under these circumstances.

---

[1] "Cyst-passer" is here used in the place of "carrier," a term which is not applicable to *E. histolytica*

In Faust's opinion the conception of amœbic invasion of the human bowel should include milder types of tissue damage. In a series of accidental deaths in New Orleans thirteen cases of *E. histolytica* infections were disclosed, of which seven showed amœbic lesions. There were three types :—(1) initial pinpoint ulceration, (2) shallow crater-like lesions, (3) extensive very shallow denudation of the mucosa. None of these destructive processes extended beneath the muscularis mucosæ.

The lesions of the mucosa may actually be microscopic. Cytolysis and necrosis of the epithelium is followed in the majority of instances by rapid regeneration, so that probably only a small percentage develop clinical evidences of amœbic dysentery. The experiments of Walker and Sellards showed that out of 20 men fed with *E. histolytica* 18 became parasitized, but only 4 developed dysenteric symptoms, though the remainder continued to pass cysts in their stools.

By intrarectal and intracæcal injection of fæces containing cysts into cats and puppies, ulceration of the bowel-wall and hepatic abscesses have been produced ; but, although the fæces may be swarming with active vegetative forms, no cyst-formation has ever been observed in these animals. Similar lesions have been produced in kittens by intrarectal injection of cultures of *E. histolytica.*

Infection in carriers of *E. histolytica* is remarkably persistent and, in all probability, unless cured by anti-amœbic treatment, these persons continue to pass cysts for the remainder of their lives.

Craig and other American authorities believe that everyone who harbours *E. histolytica* cysts is a candidate for some more serious complication and that therefore every " carrier " should receive adequate treatment.

Incidence of cyst-passers or carriers.—Among British soldiers after a year's service in Egypt, Wenyon and O'Connor found that there was no marked difference between carriers who had previously suffered from dysentery and those who had not (the percentages being 6·5 as against 4·5 per cent.). The carrier rate among native Egyptians, as might be surmised, was considerably higher, 13·5 per cent. The most surprising outcome of the systematic examination of fæces by protozoologists during the 1914–1918 war was the almost universal presence of the histolytica carrier. Yorke, Matthews and Malins Smith found a considerable percentage of carriers among lunatics, army recruits, and the personnel of the navy in England. The two former recorded 5 per cent., the latter 19 per cent. ; Kuenen found a considerable number of indigenous infections in Holland, and Brug estimated the carrier-rate as 12·7 per cent. in that country. In the United States amongst schoolchildren it may be as high as 10·8 per cent., but in adults Andrews and Paulson gave a much lower figure, 0·2 per cent. In New York City it is 1·1 per cent. among city dwellers, and 5·4 per cent. among foodhandlers, and in Philadelphia 5·2 per cent. for the general population. Craig has estimated that 10 per cent. of the total inhabitants of the United States are infected with amœbiasis. The exact significance of these figures is difficult to determine. It certainly does not mean that this comparatively large number is suffering from gross ulceration of the bowel, for indigenous *amœbic dysentery* is almost unknown in England. Even among the insane, with a relatively high cyst-passer rate, "clinical amœbic dysentery" is rare.

Pathology.—The earliest lesions of amœbic dysentery are minute yellow hemispherical elevations of the mucosa, which mark the site of a deeper-lying zone of necrosis. By growth in size and localized necrosis they form flask-shaped ulcers, the bases of which lie in the submucosa. These ulcers are scattered throughout the large intestine, rarely extending above the ileo-cæcal valve. The appendix may be involved, and Musgrave, in 1910, reported three cases of fatal peritonitis due to this; since then a few other cases have been investigated in which entamœbæ were demonstrated in microscopic sections. Amœbic ulceration of the ileum was described by Biggam. These were acute and rapidly fatal cases, and in neither instance were amœbæ demonstrated in the stools but only in preparations from the lesions. Active amœbæ and cysts were found in the duodenal juice in one patient in Germany.

The ulcers may not be larger than a pin's head or may measure an inch or more in diameter, and, as the disease progresses, may become even larger. Then the margins are rolled, the edges undermined, and the base is formed by fibres of the muscular coat (sea-anemone ulcers). The ulcers are capped by dense yellow, green, or even black sloughs (Dyak-hair sloughs), which may project into the lumen of the bowel. The lesions usually originate in the cæcum, and are scattered throughout the transverse and sigmoid colon and rectal canal, though the intervening mucous membrane remains healthy. Amœbic lesions commonly extend throughout the large intestine as far down as the internal anal sphincter.

In 186 cases examined *post mortem* by Clark in 1924, lesions were scattered throughout the colon in 61 per cent. affecting, in order of frequency, cæcum, ascending colon, iliac colon, sigmoid, rectum and hepatic flexure. At the sites where intestinal stasis is greatest there is a tendency for amœbæ to invade the bowel wall.

In chronic amœbiasis there is inflammation and compensatory hypertrophy of the bowel-wall. Sometimes sacculation and constriction of the large intestine may be produced by cicatrization (Plate X, Fig. 1).

Sellards and Leiva demonstrated in experimental animals that when the cæcum is exposed and infective material is introduced into the lumen, infection takes place with surprising regularity, but that, whether it is introduced directly into the cæcum or *via* the rectum, initial lesions occur in the extreme lower part of the bowel. Stasis in the large intestine affords the organisms a foothold, and is a factor in determining the location of the initial lesion. Wagner and Beiling, whose conclusions are almost identical, found that the amœbæ at these focal points enter the tissues in one of three ways, passing directly into connective tissue, crypts, or lymph-channels, where they migrate to the lymph-follicles and the submucosa. The intestinal mucosa responds to invasion by secreting mucus, which, when mingled with blood, forms an excellent medium for the development of amœbæ on the bowel surface. The balance between host and parasite is delicate.

Thrombosis of the blood-vessels, in which entamœbæ are often found, occurs at the bases of the ulcers, and, by erosion, an arteriole may be opened, and rarely severe or fatal hæmorrhage result. Perforation by ulcers, even massive gangrene, especially of the cæcum, may occur, and lead to fatal peritonitis.

In the healing gut, cicatricial pigmented scars mark the sites of former ulcers. Adhesions may form between proximal coils of intestine which become matted together or adherent to the liver and spleen. Pericolic abscesses may sometimes form.

In chronic cases, polypoid or gangrenous tags project into the lumen of the gut. The intestinal contents may be composed of dark, almost black hæmorrhagic fæcal matter with characteristic penetrating odour.

Carcinoma may originate at the site of healed amœbic lesions.

The cadaver shows no signs of toxic absorption, such as occurs in the bacillary dysenteries. Apart from wasting, the other viscera exhibit few, if any, changes.

Histology.—The amœbæ work their way down the crypts of Lieberkühn, multiply, and, by secretion of cytolysins, disintegrate the tissues of the submucosa and produce gelatinous necrosis, with a little surrounding tissue reaction and round cell infitration (Fig. 69). In more advanced lesions the entamœbæ may be seen between the muscular fibres and within the peritoneal veins, whence they may be swept as emboli into the portal vein, lodge in the liver, and so become the starting-point of an amœbic hepatitis or liver abscess.

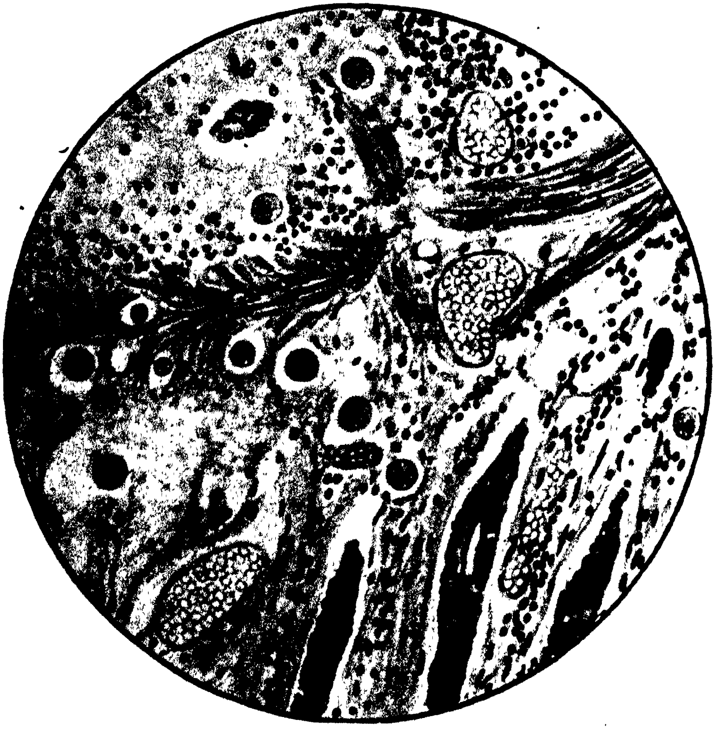


Fig. 69.—Section through base of amœbic ulcer, showing *E. histolytica* in the tissues. (*C. M. Wenyon*)

The superficial layers of the slough of an amœbic ulcer become secondarily invaded by bacteria, though the adjacent mucous membrane remains healthy and shows few microscopic changes. The precystic forms of *E. histolytica* are found in the intestinal mucus and on the surface of the bowel.

Experimentally-produced amœbic dysentery in kittens differs essentially from the disease seen in man. When introduced into the rectum of the cat, entamœbæ produce, within two to three days, acute inflammation. The lesions differ in their generalized and acute character from those observed in man. Death takes place from secondary terminal bacterial invasion. Cysts are never found, and chronic ulceration does not occur.

Symptoms.—The *incubation period* of amœbic dysentery, from the time of introduction of the cysts into the intestinal canal until the development of symptoms, is of considerable length. In the Chicago outbreak of 1933 it ranged from seven up to seventy-seven days, symptoms appearing occasionally within one week though, in a few instances, not for three or four months. The fact that amœbic cysts are found in the fæces of individuals who may never have had " dysentery " in the ordinary accepted sense, suggests that the development of clinical symptoms depends upon some secondary bacterial infection.

The great majority of cases of amœbic dysentery run a chronic course, with frequent intermissions and relapses. This latency is one of the most striking and characteristic features of amœbic dysentery. The *onset* is generally insidious, so that the patient may complain more of diarrhœa than of dysenteric symptoms. Perforation of the bowel, leading to fatal peritonitis, has been known to occur in patients who, judged by clinical data, were not suffering from dysentery. In mild cases the patient generally complains of suddenly developed *amœbic diarrhœa.*

The symptoms, subjective and objective, may resemble those of bacillary dysentery ; but, as a rule, abdominal tenderness is much less acute, and may be restricted to the cæcum, where it may simulate appendicitis, or to the transverse colon, where it may mimic gastric ulcer ; more frequently it is limited to the sigmoid flexure. Should ulceration occur in the rectum, tenesmus and straining may be noted. The individual stools are larger than those of bacillary dysentery. They may not exceed three or four in the twenty-four hours, and are seldom more than twelve. As a rule, they contain much dark and altered blood, which imparts a penetrating, disagreeable odour. In consistence and appearance they resemble *anchovy sauce.* Often, blood-streaked mucus is intermingled with liquid fæces. Melæna may occur occasionally. The motions may be formed, and streaked with blood and mucus. Gangrenous sloughs may be voided. Unless the case is complicated by hepatitis, when the liver is painful and enlarged, there are seldom any toxic manifestations. *Acute* cases of amœbic dysentery with high fever and urgent painful and severe clinical manifestations are rare. In the Chicago epidemic acute cases of unusual severity, with pyrexia and other toxic manifestations (amœbic fever), were noted.

The patient, as a rule, becomes emaciated, but some remain in remarkably good condition, although suffering from repeated relapses. The Editor has seen patients, suffering from chronic amœbic dysentery, become grossly fat. Sometimes the skin is myxenoid and the complexion has a subicteric tinge. The tongue is moist and coated. Vomiting may rarely occur. Generally there is a complete anorexia. Dysuria is not noted as in bacillary dysentery, and *tenesmus* is rare. The *liver* is sometimes enlarged, even in the absence of hepatitis.

In uncomplicated amœbic dysentery there is no pyrexia, but cases with periodic rigors, suggestive of malaria, are occasionally met and may be recognized by amenability to emetine treatment and by discovery of amœbic cysts in the fæces. In amœbic dysentery there is usually a moderate leucocytosis (10,000–12,000 with low proportion of polymorphonuclears—about 70 per cent.).

There still remain a number of obscure conditions of which some mention must be made. It is probably true, so variable are the symptoms of amœbiasis, that almost any intestinal disease may be simulated. Intestinal amœbiasis is *not invariably associated with dysentery or diarrhœa.* It may occasionally be marked by constipation, by intestinal pains or disturbances, very often by neurasthenia, bodily and mental lassitude, furred tongue, and disordered digestion, popularly described as an "uncomfortable belly," or "growling abdomen." In these cases discovery of amœbic cysts in the fæces, followed by appropriate treatment, may improve the clinical condition. Pathological changes in the bowel may sometimes lead to sacculation or even dilatation of the colon. Very often the cæcum is grossly distended with gas and the source of much discomfort. In chronic cases, infiltration of the sigmoid colon, less commonly of the cæcum, can be detected by abdominal palpation.

In the course of chronic amœbiasis cachexia ensues, resembling intestinal toxæmia. These patients have muddy complexions resembling in outward appearances some cases of diverticulosis.

Often, without treatment, symptoms may subside, and the patient may be apparently cured, but will relapse after an interval of weeks, months, or even seven years or longer. More often he continues to pass loose, semi-formed stools. Attacks of diarrhœa alternate with constipation. After any physical exhaustion, chill, alcoholic or dietetic indiscretion, a fresh exacerbation may supervene. On account of these variable symptoms, the infinite variety of abdominal pain, and the occasional melænic stools, it is clear that amœbic dysentery has to be differentiated from duodenal ulcer, gall-bladder disease, pancreatitis and neoplasm.

Hepatitis.—Acute amœbic hepatitis may supervene at any time during the course of amœbic infection, while the symptoms are acute, or during a remission. The patient usually experiences great pain over the hepatic area[1], together with signs of toxæmia and considerable pyrexia. The liver itself is enlarged; it may project below the costal margin to the level of the iliac crests, and be extremely tender. Pain referred to the right shoulder is also frequent. Usually there is a leucocytosis of twenty to thirty thousand with low proportion of polymorphonuclears.

Hepatitis may subside without any active treatment. There is some evidence that in these cases the amœbæ are distributed throughout the liver, with embolic spread, suggesting a portal distribution. Fortunately it is particularly amenable to emetine treatment (*see* p. 517.)

: : he inclines to the right and tries to protect his liver. He carries it in his hands, so to speak.

Complications.—Death may result from exhaustion, intestinal hæmorrhage, perforation, or liver abscess.

The most frequent complication of amœbic dysentery is liver abscess.

Perforation of the bowel may be sudden, or be preceded by intense local pain, which, when restricted to the right iliac fossa, may be mistaken for appendicitis. Occasionally, pericolic abscess may be produced, especially in the descending or sigmoid colon. Intestinal obstruction from an amœbic granuloma (amœboma) has been recorded, and when this forms in the cæcum it may resemble hypertrophic tuberculosis or malignant disease.

Amœbiasis may be superimposed upon bacillary dysentery, or *vice versa*. In Egypt, intestinal amœbiasis is often found associated with *Bilharzia mansoni*. Visceroptosis, distension or sacculation of the gut, leading to intestinal stasis, may constitute distressing results of amœbic dysentery, but stricture of the rectum does not ensue. *Appendicitis* due to amœbic ulceration is not uncommon. Snapper has recorded a psoas abscess as the result of perforation of an amœbic ulcer of the cæcum.

Sequelæ.—Many sequelæ of intestinal amœbiasis have been described. often on insufficient evidence, and it is very difficult to prove direct association of different obscure clinical states with a past infection with *E. histolytica*. The Editor believes that certain intestinal conditions occur frequently as the aftermath of amœbiasis; such are appendicitis (not necessarily caused by amœbic ulceration), mucous colitis, and *duodenal ulceration*. Chronic amœbiasis, besides producing chronic ill-health, very often contributes to introspection and neurasthenia.

Diagnosis.—It is safe to regard acutely developing tropical diarrhœa either as bacillary or amœbic dysentery, though clinical distinctions in the less acute manifestations are often unreliable. Assistance in diagnosis may be obtained from the more rapid onset, the febrile condition. and the rapid pulse in the bacillary disease. As a rule, the number of stools in bacillary dysentery is greater and their individual size less. The character of the stools should also be taken into account. Usually they contain more dark blood in amœbic dysentery. Occasionally, however, they may be tarry, suggesting duodenal ulceration.

Laboratory diagnosis should always be resorted to, having regard to the experience of the observer and his ability to determine whether any amœba-like body discovered in the fæces is in fact *E. histolytica*, *E. coli*, or some large tissue cell, such as a macrophage (Plate XI). With practice this becomes comparatively easy. Entamœbæ may be absent in some portions of a stool, numerous in others. Several preparations must be searched, at first with the ⅔-in. lens, subsequently with the ⅙-in. Whenever possible, a portion of blood-stained mucus must be picked out for examination. The organisms may be difficult, or almost impossible, to detect in a specimen containing too much blood. It is important that the specimen should be as fresh as possible. The discovery of an active amœba containing ingested red blood-corpuscles is generally sufficient to establish the diagnosis of *E. histolytica*. In the more chronic and latent forms of the disease the characteristic cysts must be sought. Entamœbæ and their cysts can at first be recognized under a low-power lens as " bright stars," of higher refractility than other cells, especially with the eosin contrast method whereby the background is stained pink whilst cysts stand out as clear refractile objects. Examination should not be considered as completely excluding an amœbic infection until the stool has been searched on *each of seven* consecutive days. Cultural methods may assist diagnosis in scanty infections.

In cases in which there is any doubt of the identity of the cysts,[1] they may be stained by the rapid, or by the more prolonged iron-hæmatoxylin method (p. 1012). Mixing the fresh fæces with a solution of Weigert's iodine (p. 1012) brings out nuclei and other characteristics.

Charcot-Leyden crystals are commonly found in the fæces in amœbic dysentery, and their presence has been regarded as of diagnostic importance. The crystals vary very much in size, averaging 5–25 μ; their typical shape resembles a whetstone, and they are soluble in warm water, strong mineral acids, and alcohol. They may also be found in preparations from amœbic ulcers, made through the sigmoidoscope (Plate XII).

The Editor emphasizes the danger of attaching too much importance to Charcot-Leyden crystals as necessarily diagnostic of intestinal amœbiasis. He has found them in malignant disease of the rectum, mucous colitis, coccidiosis (*Isospora hominis*), ulcerative colitis, and various helminthic infections (*see* p. 1011).

Complement-fixation reaction (Craig).—Craig described a technique for the preparation of amœbic antigen and for carrying out this test, which is practically the same as that used for the Wassermann reaction. The antigen is an alcoholic extract of cultures of *E. histolytica* grown upon a modified Boeck-Drbohlav medium. A rich culture is selected and from this at least 120 sub-cultures are made. Then all the material at the junction of the egg slant with Locke's serum solution is pipetted into suitable tubes, centrifuged and the sediment extracted in the incubator at 37° C. for fifteen days with seven and a half volumes of absolute alcohol. Craig has now published results from 1,000 cases in which diagnosis was checked by the fæces examination. Of those giving a positive reaction (175), *E. histolytica* or cysts were found in the fæces of 89·7 per cent.

Meleney and Frye have tested the value of complement-fixation in experimentally infected animals inoculated parenterally with amœbic extracts. Experimentally infected dogs and monkeys usually gave a positive reaction.

Intradermal test.—The intradermal test of Scalas is as follows: the test material is obtained by mixing mucus containing *E. histolytica* with 30 c.c. of physiological saline solution, and incubating the result for one week at 37° C. with daily shakings and decolorization with animal charcoal. In positive reactions an indurated swelling at the site of inoculation is produced.

Sigmoidoscopic examination.—Amœbic ulceration may extend into the rectal canal, so that sigmoidoscopic examination, conducted without an anæsthetic, usually affords valuable information. Quite commonly, small yellow ulcers with surrounding hyperæmia are seen, especially in the region of Houston's valves. It is often possible to find living entamœbæ in the scrapings, even when they cannot be demonstrated in the fæces[2]. In contrast to chronic bacillary dysentery, instrumentation is practically painless. Amœbic ulcerations may be touched or scraped without causing any painful sensation. The mucous membrane surrounding individual lesions shows absence of inflammation, preserving its normal pink colour, but it is usually more reticulated and folded than normal.

---

[1] Concentration may also be employed for recognition of *E. histolytica* cysts (p. 1012).

[2] By this method the Editor has diagnosed amœbiasis in a case resembling enteric fever.

Amœbic lesions are then seen in the crypts between the folds, either as small, yellow elevations the size of a pin's head, or as superficial snail-track ulcers with hæmorrhagic margins (Plate XIII). Often the only signs of abnormality are small, flame-shaped hæmorrhages, in the centre of which the entamœbæ may be demonstrated in scrapings obtained by means of a long-handled Volkmann's spoon passed through the sigmoidoscope (Fig. 70). A porcupine quill forms a convenient instrument for transferring material from the spoon to the microscope slide.

In the Editor's series of 535 cases of intestinal amœbiasis, 509 were diagnosed by microscopic examination of fæces, in the remainder by demonstration of amœbæ in scrapings from amœbic ulcers. Out of 258 sigmoidoscopic examinations, characteristic amœbic lesions were demonstrated in 234.

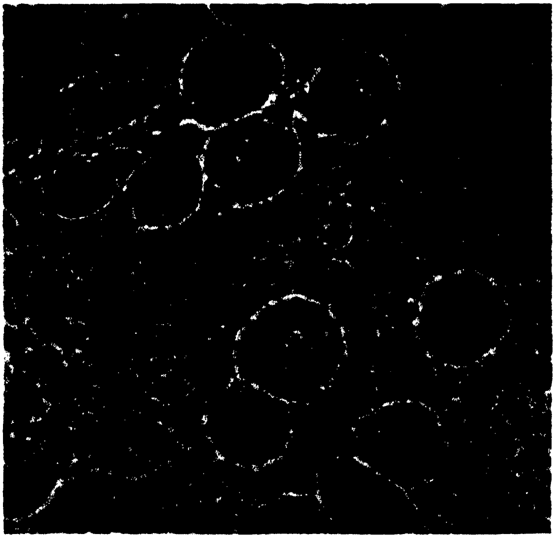


Fig. 70.—Amœbic dysentery, showing tissue-invading *E. histolytica* in scrapings of ulcer obtained through the sigmoidoscope.

In chronic, partially-healed amœbic dysentery, or even in symptomless cyst-passers, amœbic lesions may be distinguished as minute oval circular pits, or depressions, irregularly disposed. They may be almost microscopic, requiring a magnifying eye-piece for their detection. Occasionally solitary amœbic ulcers, resembling carcinoma, are seen in the rectum, twenty years or more after the primary infection. Fungating granulomatous masses (amœboma or amœbic granulomata) may be discovered.

X-rays in diagnosis.—Vallerino described, as indicative of amœbic lesions, filling defects in cæcum and ascending colon with deficient haustration of the bowel, seen after a barium meal, but not so easily after an opaque enema. X-ray diagnosis has been tried on an extended scale at the Hospital for Tropical Diseases, London. Occasionally filling defects have been observed in the cæcum, but similar appearances are seen in other forms of dysentery and colitis. Only unsatisfactory assistance can be obtained by this method.

Differential Diagnosis.—Differential diagnosis has to be made from many other conditions in which blood and mucus are passed in the stools, and this means differential diagnosis from all other forms of dysentery, colitis, or even other forms of intestinal disease. Differential diagnosis from malignant disease of the bowel deserves emphasis. Many observers—James, Willmore, Gunn, Howard, Haran and Mendelson—have described a hypertrophic form of intestinal amœbiasis—amœbic granuloma—which may affect different portions of the large bowel, cæcum, or sigmoid, and which may produce tumours 12 by 10 cm. in extent, and on account of these physical characters may resemble carcinoma and cause partial occlusion. The process consists primarily of an isolated ulcer, with progressive erosion of the bowel-wall in response to long-continued secondary infection. Gelatinous granulation tissue appears, and the process may affect the bowel-wall and neighbouring mesocolic fat with enlargement of the mesenteric glands. Satisfactory diagnosis can usually be made by microscopic examinations of scrapings or by removing tissues by biopsy when entamœbæ may be demonstrated in sections. This also applies to the solitary ulcers described on p. 491.

TREATMENT

Many diverse drugs have been advocated for amœbic dysentery. Treatment requires careful supervision. Specific drugs may be preceded by a purge ; castor oil is the most appropriate. Opium, as a routine measure, should be avoided. The dietary should be carefully regulated and, in the acute stages, nursing is important. As all drugs used in the treatment of amœbiasis contain toxic principles, especially emetine and its derivatives, a definite diagnosis of amœbiasis must be made before they are exhibited. Unfortunately there is a reprehensible tendency to inject emetine indiscriminately as a diagnostic measure in all cases of dysentery.

Ipecacuanha.[1]—It had long been recognized in India and in the Far East that ipecacuanha root was a valuable drug in chronic dysentery ; this was Manson's opinion based upon a wide experience in China. Its use is now a matter of history, though it is sometimes employed and is still beneficial in the after-treatment of liver abscess or pulmonary amœbiasis (*see* p. 523). Food should be interdicted for three hours, and then 10 to 20 drops of laudanum given in a tablespoonful of water, and a mustard plaster applied to the epigastrium to counteract the emetic effects of the drug ; about twenty minutes later, when the patient is under the influence of the laudanum, 20 to 30, and even as much as 60 gr. of ipecacuanha, in pill, bolus, capsule, or suspension in half a wineglassful of water, are administered. The dose of ipecacuanha must be continued daily for at least a week.

I. Emetine.—There are four alkaloids of ipecacuanha—emetine, cephæline, psychotrine, and emetamine, but only the first-named has definite therapeutic properties. Emetine should be injected subcutaneously or intramuscularly. It is apparently a toxic drug, especially to children and women, when given *intravenously* or in excessive doses. It is a white crystalline powder, sensitive to light, soluble in four parts of water, and highly irritant to the eye.

Dobell showed that emetine is lethal to amœbæ in culture, a strength of one in five million. Nossina proved that this action is influenced by the acidity of the medium. It has a slight action in an acid medium, but the effect increases as the reaction approaches neutrality. The optimum is *p*H 6·8. Cephæline is far less effective. It is curious that emetine and cephæline, though pre-eminently active in preventing multiplication of *E. histolytica*, do not apparently exert any direct action. On the other hand, a derivative of emetine—dimethoxyemetine, which has a potent direct action, fails to cure the infection in man.

---

[1] Brazilian ipecacuanha root (*Cephaelis ipecacuanha*) is said to be more efficacious than the preparation from New Grenada (*Uragoga granatensis*), as it contains more emetine.

In large doses, more than 1 grain a day, emetine is apt to produce toxic symptoms. It may lead to asthenia, cardiac irregularity, emaciation, mental depression, and in rare cases to myositis and even neuritis which may affect a particular group of muscles and produce partial paralysis. Thus, the Editor has seen atrophy of the scapulo-humeral group, resembling chronic poliomyelitis. In excessive doses it may actually produce diarrhœa. Emetine therapy is frequently followed by fine branny desquamation of the skin and an atrophic brittle condition of the nails. (Fig. 71.) Emetine injections exert no action on the pre-cystic forms of *E. histolytica*, and are therefore ineffective in chronic cases with cysts in the fæces.

Fig. 71.—Effect of emetine intoxication on the nails : increase of lunule, striation and brittleness. (*Dr. T. Jackson*).

Attention must be paid to the toxic manifestations of emetine when given injudiciously without proper indications. Being a cytoplasmic poison it is especially toxic when given to patients with bacillary dysentery. Apart from its general toxic action on the tissues, it has an especial affinity for the heart. This action has been shown by Epstein to be on the myocardium and the conducting fibres, and it may produce auricular fibrillation[1]. Improperly-conducted emetine injections, especially in debilitated persons, may produce fixation abscesses or widespread cellulitis, and the Editor has seen two cases where this was so extensive that the patient nearly lost his arm. Eczema, or even ulcers, may be provoked at the site of injection. Often the stiffness and irritation resulting from emetine injections are intolerable. Most of these drawbacks may be obviated by giving intramuscular injections. Emetine is specially toxic to young children and is mentally depressing to adults. It should not be injected intravenously.

---

[1] By electrocardiographic methods Heilig and others have shown that the cardiac effects have possibly

It should never be given hypodermically to patients who are leading an active life or taking hard physical exercise. This rule is too frequently disregarded, and permanent cardiac damage is the result.

It is best to initiate treatment with a course of deep subcutaneous or intramuscular injections of emetine hydrochloride (1 gr. in 1 c.c. of distilled water) daily for ten or twelve days. This does not suffice to eradicate the infection from the bowel, as the Editor has shown. It should therefore be supplemented by a course of the *double iodide of emetine and bismuth* (emetine-bismuth iodide). Emetine[1] injections are much more effective in *metastatic amœbic lesions* (hepatitis, etc.) than in intestinal amœbiasis.

The prevailing practice of giving periodic courses of emetine injections in chronic amœbiasis is subject to serious objections in so far as it tends to render *E. histolytica* emetine-fast and to make further treatment ineffectual. The renewed practice nowadays of giving heroic courses of emetine does not eradicate the infection but poisons the patients.

II. Emetine-bismuth iodide was introduced by Du Mez in 1915 and later it was popularized by Dale. It contains 58 per cent. of iodine and 28 per cent. of emetine. In the intestine the insoluble salts of bismuth are converted into bismuth sulphide after passing the pylorus. It is indicated especially in chronic cases and in persistent passers of *E. histolytica* cysts and is given by the mouth. More usually known as E.B.I., it is an insoluble powder, from which the emetine is set free by contact with the intestinal juices. It was formerly said not to be decomposed in acid solution (e.g. gastric juice), but this is incorrect. It passes through the intestinal canal unabsorbed, if compressed into a hard tablet, or if coated with some insoluble substance, such as paraffin, vaseline, resin, keratin, or stearin. It is best made up in powder form in gelatin capsules (*Slipules*), or mixed with jam or syrup. The maximum individual dose for an adult is 8 gr. (0·2 grm.) per diem for ten to twelve consecutive days. Experience has shown that individual doses of 2 gr. suffice and that a total dosage of 20 gr. will entirely eradicate infection. For delicate individuals and women the dose should begin at 1 gr. and be gradually increased. This drug is more easily tolerated in temperate climates than in the tropics.

The drug is dispensed as a red powder; the capsules of gelatin are manufactured as *Slipules*. No. 5 size capsule will contain 1 gr. of E.B.I. If the full dose is given, it is better from the point of view of the patient to take one capsule containing 2 gr., but when treatment is commenced with smaller doses the patient becomes gradually accustomed to the drug.

If gelatin capsules have been kept for some time, they tend to harden and become insoluble. They should therefore be pricked with a pin before being administered.

It is important to observe certain precautions in giving this drug. When given at 10 p.m., the last solid food should be taken at 6 p.m. The patient should remain at rest; he should endeavour to go to sleep, and any saliva should be wiped from the mouth.

---

[1] Disagreeable sequelæ of emetine injections may be avoided if the skin is pinched and the inserted *deep subcutaneously*.

Vomiting and diarrhœa are to be expected in the earlier part of the course, and are to be viewed as an indication that the drug is being absorbed. Diarrhœa is a necessary prerequisite to cure, because precystic forms of *E. histolytica* live on the mucous surface of the bowel where they are not affected by hypodermic emetine but are killed by the alkaloid in the lumen of the bowel[1]. If no symptoms of nausea supervene, it is probable that the cachets are not being dissolved and their contents freed. It is necessary for the patient to remain in bed and take a liquid or milk diet with eggs and toast.

Excessive vomiting and nausea may be mitigated by 10–15 min. of *tinct. opii* given half an hour previously, or, in some patients, by nepenthe, luminal, allonal, or chloretone. Most patients lose about 5 lb. in weight while under treatment. The condition of the heart and pulse should be noted daily, but treatment should not be discontinued unless depression becomes severe. Almost invariably a fall in blood-pressure (about 20 mm. of mercury) ensues. Alcohol in any form should be prohibited. When the cure is completed the patient should be gradually permitted to resume activity, though dieting (*see* p. 504) may still be necessary.

For relapsing cases it was formerly considered necessary to give more than one course of E.B.I. and some cases were thought to be due to amœbæ which had become resistant to emetine. Too much reliance should not be laid on isolated fæces examinations, on account of the vicarious appearances of cysts, but it is advisable to re-examine fæces microscopically at the end of six weeks. The results of treatment are much better controlled by periodic sigmoidoscopic examinations. For some considerable time after disappearance of active lesions, small pits or depressions of the mucous membrane may be seen.

A modification of E.B.I.—emetine periodide (E.P.I.)—is less toxic. It may be given in capsules in dosage of 3 gr. daily, in conjunction with capsules of dried ox-bile, gr. 5, which facilitates liberation of emetine. The Editor prefers E.P.I. for those who cannot tolerate E.B.I.

Auremetine (Willmore and Martindale) is a combination of emetine with auramine (a dye). It is given by the mouth as a dark-maroon powder which is insoluble in water. It is less easily decomposed than E.B.I. in the gastric juice. The dose, 1 gr. in gelatin capsules (slipules), is given four times daily on alternate days for seven days, and then daily until a total of 40–60 gr. has been taken.

III. Iodine-oxyquinoline-sulphonic-acid preparations (*Quinoxyl*) —Sodium-iodoxy-quinoline sulphate is also known as *Chiniofon* (B.P.), *Yatren* (Bayer), *Quiniosulphan* (May & Baker), *Anayodin* (U.S.A.)[2] and *Dysentulin* (German). It is a mixture of four parts of 7-iodo-8-hydroxy-quinoline-5-sulphonic acid, containing not less than 26·5 per cent. combined iodine, and one part of sodium bicarbonate. There is some chemical reaction, so that the preparation may contain a small amount of sodium hydroxyquinoline sulphonate, in addition to sodium bicarbonate and iodohydroxy-quinoline sulphonic acid. In solution 100 parts of quinoxyl yield approximately 85 parts of iodohydroxyquinoline sulphonate. Quinoxyl can be given either by the mouth or by retention enema. By the former route the maximum daily dose is 1 grm. (15 gr.) in powder form, in capsules, or keratin-coated pills, for ten days. After an interval of one week this course should be repeated. The drug is excreted in the urine, and can be recognized by the oxyquinoline test (green colour with perchloride of iron). Quinoxyl in pill form (4 gr. each), acts best when acute symptoms of amœbiasis have been controlled by emetine. The maximum dose is four a day.

---

[1] The underlying idea of E.B.I. therapy is that emetine should reach the large intestine unabsorbed. This problem has never been properly solved. Tests for emetine in the urine should be performed after emetine has been given hypodermically or by the mouth. Similarly, fæces of patients taking various modifications of E.B.I. should be extracted. Snelling's reaction for emetine consists of adding a few drops of HCl to potassium chlorate, which, with emetine, gives an orange red colour which soon changes to violet.

[2] A somewhat similar compound is iodochloroxyquinoline or vioform, which has proved effective in monkey amœbiasis (Leake)

To obtain permanent therapeutic results, quinoxyl should be given as rectal injections (retention enema), as well as by the mouth. By this method it exerts an effective amœbicidal action. The bowel must first be washed out and cleared of mucus by an enema (1 pint) of 2 per cent. sodium bicarbonate at 8 a.m. One hour later 227 c.c. (8 oz.) of a 2·5 per cent. solution of quinoxyl, in warm water, is introduced through a stout rectal tube. The patient should be encouraged to retain the solution as long as possible, from 8 to 10 hours. The solution is then returned as a greenish liquid containing mucus and débris derived from the bowel. The course of rectal injections is continued for ten days. The foot of the bed must be raised on blocks. The course may be repeated two or three times with a week's interval between each. Dieting and rest in bed are absolutely necessary. In resistant cases higher concentrations, up to 3·5 per cent. of quinoxyl, can be given by retention enemata.

IV. Combined synergic treatment.—In the Editor's opinion this method of treatment gives far the most satisfactory and permanent results. He has tested it out now in over 600 cases of proven intestinal amœbiasis during a period of twenty years. There have been two relapses in the series, both of which have been subsequently cured by further treatment. This treatment embodies the effects of quinoxyl and E.B.I. treatments given in combination. E.B.I. acts on the amœbic lesions in the upper portion of the large intestine, quinoxyl on ulcers and lesions situated in the lower portion. It is necessary that the patient should be *at rest* and *in bed* the whole of the ten days of this treatment. Due attention must be paid to the dietary. It is not necessary to give more than a total of 20 gr. of E.B.I. and the maximum individual dose should not exceed 2 gr.

SCHEME OF DIETARY AND COMBINED TREATMENT FOR INTESTINAL AMŒBIASIS

7 a.m., pot of tea and 2 oz. milk.
7.30 a.m., one egg, buttered toast, cup of tea and 2 oz. milk.
8 a.m., sodium-bicarbonate enema, 2 per cent., 1 pint.
8.30 a.m., quinoxyl 2½ per cent. by rectum (8 oz.).
9 a.m., 8 oz. milk.
10.30 a.m., juice of an orange, glucose ½ oz.
12 noon, liver soup, chicken or fish, toast, butter, custard or milk jelly, baked apple.
4 p.m., boiled egg, toast, butter, juice of one orange and ½ oz. glucose, grapes or ripe banana, sponge fingers.
5 p.m., quinoxyl enema voided.
6 p.m., 8 oz. milk; bath.

9.30 p.m., sedative (luminal gr. 1).
10 p.m., E.B.I. (gr. 2).
10.30 p.m., sleep.
2 a.m., vomit (pharmacological action of E.B.I.).

During combined treatment the patient should be nursed in bed and should be allowed to get up for his bath. He may be allowed to use a night commode for stools and for voiding the residue of the quinoxyl enema. On the first night E.B.I., gr. 1, is given; subsequently, gr. 2.

After the completion of treatment, the patient must be permitted two days' rest to regain his strength, as a sense of weakness or stiffness is produced in the limbs; but, if carefully carried out, this treatment is not specially exhausting.

Medicinal treatment following the combined course.—An after-course of quinoxyl pills is prescribed, one or two at night for the next three weeks, according to the age and condition of the patient. These are good aperients and probably act by keeping the bowels relaxed. If the patient is much debilitated, one tablet of stovarsol is indicated daily, for 14 days.

Other methods of treatment.—*Stovarsol* (*Acetarsol*), an arsenical preparation (3-acetylamino-4-hydroxyphenyl-arsonic acid), containing 27·2 per cent. of arsenic, has been advocated, mainly in France, as an amœbicide, and has been widely used in the treatment of amœbic dysentery in combination with other drugs. It has a feeble amœbicidal action, but stimulating properties. Its special use is in the after-cure of amœbiasis. It is dispensed in 4-gr. tablets, but the maximum dose is two daily for one week to ten days, but not longer; in sensitive persons not more than one tablet daily is advisable. This drug has to be carefully watched, as it may give rise to a toxic erythema with pyrexia resembling German measles, and even to exfoliative dermatitis. None of these arsenical drugs should be administered to patients in whom liver damage is suspected. A delayed papular toxic rash has been seen three weeks or so after the administration of the drug. Other varieties are known as *Spirocid*, *Orarsan* (Boots) and *Halarsol* (May & Baker).

Carbarsone (Eli Lilly & Co.), 4-carbamino-phenyl arsonic acid, ($H_2O_3AsC_6H_4NHCONH_2$), was originally prepared by Ehrlich and contains 28·8 per cent. of arsenic. It has been much used in America and is given in the same manner as stovarsol, and has apparently the same therapeutic properties and the same indications. Most American authorities advise a dose of 0·25 grm. twice daily in capsules (pulvules) for ten days. Both stovarsol and carbarsone may be administered *per rectum* in the form of retention enemata of 2 grm. in 200 c.c. of warm 2 per cent. sodium bicarbonate solution. *Amibarson* is a similar compound. All these are useful in cyst-passer cases. Sodium amytal, 3 gr., is used as a sedative.

Kurchi and derivatives.—(*a*) Kurchi *bark* (containing an alkaloid, *conessine*) was formerly recommended, in 10 gr. tablets three times daily for a lengthy period, as after-treatment in intractable cases. It apparently has no specific action. (*b*) *Kurchinine hydrochloride* (Whiffen & Sons, Ltd.), a crystalline alkaloid from kurchi bark, has been used both for oral administration and hypodermic injections in doses of ½–1 gr. on three successive days. This has been supplanted by *Kurchi bismuthous iodide* (*Anabin*) which contains the total alkaloids of the bark. According to Acton and Chopra it was given by the mouth in 10 gr. doses, twice daily for ten days without producing deleterious effects. Although the first reports were encouraging, it is not much used at present.

Ko-sam, dispensed in tabloid form by Burroughs Wellcome, is prepared from the seeds of *Brucea sumatrana* and has a reputation in the Far East.

For resistant cases passing *E. histolytica* cysts, which are now occurring, Rhoads has successfully used *phenothiazine*—12 grm. suspended in 1¼ pints of warm water, as a retention enema. Three treatments are given on alternate days and produce little or no discomfort.

Rivanol, a derivative of acridine, is injected *per rectum*, after a cleansing, non-irritating enema. It is diluted in distilled water 1 in 500 to 1 in 2000; of this 500-800 c.c. at body-temperature is administered *per rectum* with the patient lying on his side, or in the knee-elbow position. A course of ten or more treatments is necessary. Rivanol is antispasmodic and antiseptic and is useful for the relief of pain and tenesmus, especially in ulcerative colitis.

Vioform, or enterovioform (iodochlorhydroxyquinoline), is somewhat similar to iodoform and contains 37·5 per cent. of iodine. It is administered by the mouth in gelatin capsules each containing 0·25 grm. (4 gr.) of the powder, three times daily, for ten days. In chronic cases it may be injected for ten days as retention enemata, each consisting of 150–200 c.c. of warm water in which 2 tablets have been dissolved.

Diodoquin (5 : 7–diodo–8–hydroxy–quinoline) contains 63·9 per cent. iodine, and has acquired a great reputation in America. Its action is similar to that of vioform, but its absorption is more irregular and it is therefore more toxic. Tablets of 3·2 gr. are given by mouth, 10–12 a day for 20 days.

Of these preparations, carbasone and vioform have the best reputation in U.S.A. but are contra-indicated if there is any liver involvement.

Penicillin, in large doses, has a favourable effect on distressing, resistant and toxic cases, but none on the amœbæ.

Treatment of hepatitis.—During the course of amœbic dysentery, and for months afterwards, the liver must receive careful attention. It may not be possible to prevent abscess formation; but if pain suggests it, an attempt to avert this grave complication may be made by giving repeated doses of emetine subcutaneously, saline aperients, rest, low diet, fomentations, dry-cupping, and similar measures. Emetine acts much more rapidly and specifically in hepatitis than in amœbic infection of the bowel, and in some cases aspiration of the liver (hepatic phlebotomy) has a wonderful effect. Usually a total of 6 gr. of emetine suffices to overcome the more active symptoms.

Perforation of amœbic ulcer.—To avoid fatal peritonitis, diagnosis of perforation of the large bowel should be made as soon as possible. This is usually very difficult. Two successful instances during the 1914–18 war were recorded where timely operation saved the patient's life.

Other considerations.—Symptoms must be treated as they arise. Abdominal pain should be counteracted by hot applications, colic by a belladonna and bromide mixture (*see* p. 484), and tenesmus by morphia suppositories or starch-and-opium enemata.

Diet.—A suitable diet in the convalescent treatment of amœbic dysentery is important after the combined quinoxyl and E.B.I. treatment. Alcohol, unless taken in small quantities, certainly predisposes to relapse. The following diet is advocated for four weeks after active treatment:

Permitted.—Porridge; eggs; filleted or fried fish—haddock, plaice, cod, sole or whiting; toast or rusks; milk puddings—rice, sago, semolina, ground rice; spinach or young peas, vegetable marrow, cauliflower; plain cakes; fruit jellies; stewed pears or peaches; baked apples; bananas, grapes; tripe, brains, sweetbreads; chicken; rabbit; game.

Not permitted.—Cheese; new bread; potatoes; fats; suet puddings; rich cakes with raisins or spices; pastry; pickles.

Beverages.—Light wine only; no spirits, beer, or stout.
Meat.—Red meat, i.e., mutton or beef, can be permitted once daily.

Surgical measures must be reserved for complications of amœbiasis, e.g. pericolic abscess. Heroic procedures such as cæcostomy usually find no place in the treatment of intestinal amœbiasis.

Prophylaxis of amœbiasis is practically the same as for bacillary dysentery, and depends upon efficient sanitation, measures directed against the housefly, and avoidance of unboiled water, raw vegetables, or other foods which may have been contaminated by human fæces. As cysts of *E. histolytica* can only survive in a moist medium, there is a considerable amount of evidence, experimental and epidemiological, that amœbic infection is usually waterborne. The problem of dealing with human carriers of *E. histolytica* cysts is a constant difficulty. It is not likely to arise in countries equipped with a proper system of sanitation, but in no case ought a cyst-carrier to be employed as cook or mess orderly, or handle water supplies. Wherever possible, cyst-carriers should be treated by the combined method, though a prolonged course of carbarsone is sometimes effective.

Quinoxyl, in pill or tablet form (4 gr.) at night, in tropical countries where amœbiasis is rife appears to act as a prophylactic measure as well as a satisfactory aperient. Diodoquin is also recommended.

Efforts have been directed to exterminating amœbic cysts from contaminated water supplies. This cannot be done by medicating the water with chlorine or chloramine. Spector, Baylis and Gullans proved that the best method of removing the cysts is by filtration through sand-filters, combined with coagulation.

COMPLICATIONS OF AMŒBIASIS

1. HEPATIC ABSCESS (LIVER ABSCESS; HEPATIC AMŒBIASIS)

Geographical distribution.—Liver abscess of the type known as tropical abscess, for the most part a disease of warm climates, corresponds in its distribution with amœbiasis. While the entamœba is the principal element in its production, its incidence depends probably on special susceptibility of the European to this complication.

Ætiology. *Relation to amœbic dysentery.*—There can be no question of the existence of an intimate relationship between amœbic dysentery and liver abscess. Many well-authenticated statistics, as well as everyday experience, attest this. In 3,680 dysentery autopsies made in various tropical countries, and collated by Woodward, 779 (21 per cent.) revealed abscesses of the liver. Extensive amœbic ulceration may exist without exciting any subjective symptoms whatever (*see* p. 490). Moreover, many patients suffering from liver abscess forget, or fail to mention, a previous dysenteric attack, or may mislead the physician by describing such an attack as "diarrhœa," so that the relationship is much more intimate than even statistics indicate. In the great majority of cases dysentery antedates the abscess, it may be by as long as twenty years.

Race, sex, and climate.—Though common in Europeans in the tropics, liver abscess is proportionately rare among natives. Thus, in the native army of India the proportion of deaths from liver abscess to the total mortality in 1894 was only 0·6 per cent., whereas in the British army it was 7·4 per cent. Man for man, the relative liability of the European and the native soldier is as 95·2 to 4·8. This disproportion holds in spite of the fact that a larger proportion of the natives are infected with *E. histolytica.*

It is well known that European women in the tropics, though nearly as subject to dysentery as European men, rarely suffer from liver abscess, and children hardly ever. It is most common between the ages of 20 and 40, though there are records of amœbic abscesses of the liver in Egyptian children of three months of age and of others in India of ten. The youngest in the Editor's experience was an English girl of sixteen.

Pathology.—It may be inferred from the symptoms that in the early stages of suppurative hepatitis there is general congestion and enlargement of the liver; in some instances this condition may be more or less confined to one lobe or even part of a lobe. Later, as shown especially by observations on cases that have died from the attendant dysentery, one or more greyish, ill-defined, circular patches, ½–1 in. or thereabouts in diameter, are formed. These grey spots are very evident on section. A drop or two of a reddish, gummy pus may be expressed from these necrotic patches. Still later, the centres liquefy, and distinct but ragged abscess cavities are formed. An abscess thus commenced extends partly by breaking down of liver parenchyma; partly by more massive necrosis of portions of its wall; partly by the formation of additional foci of softening in the neighbourhood and subsequent breaking down of the intervening septa. The walls have a ragged and tessellated appearance. As the abscess enlarges, so the zone of necrotic tissue becomes narrower. The character of the contained pus also changes during the evolution of the abscess, and it frequently becomes secondarily infected with streptococci and other organisms, when it assumes a brownish or greenish colour.

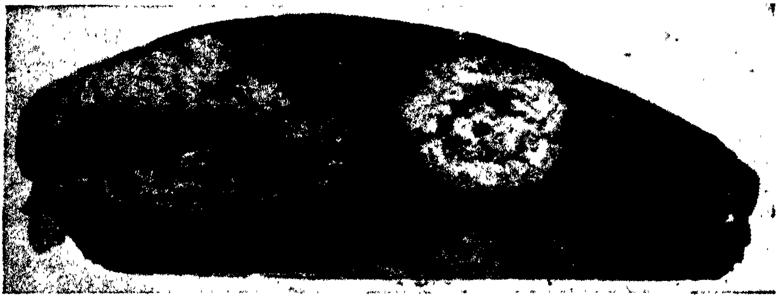
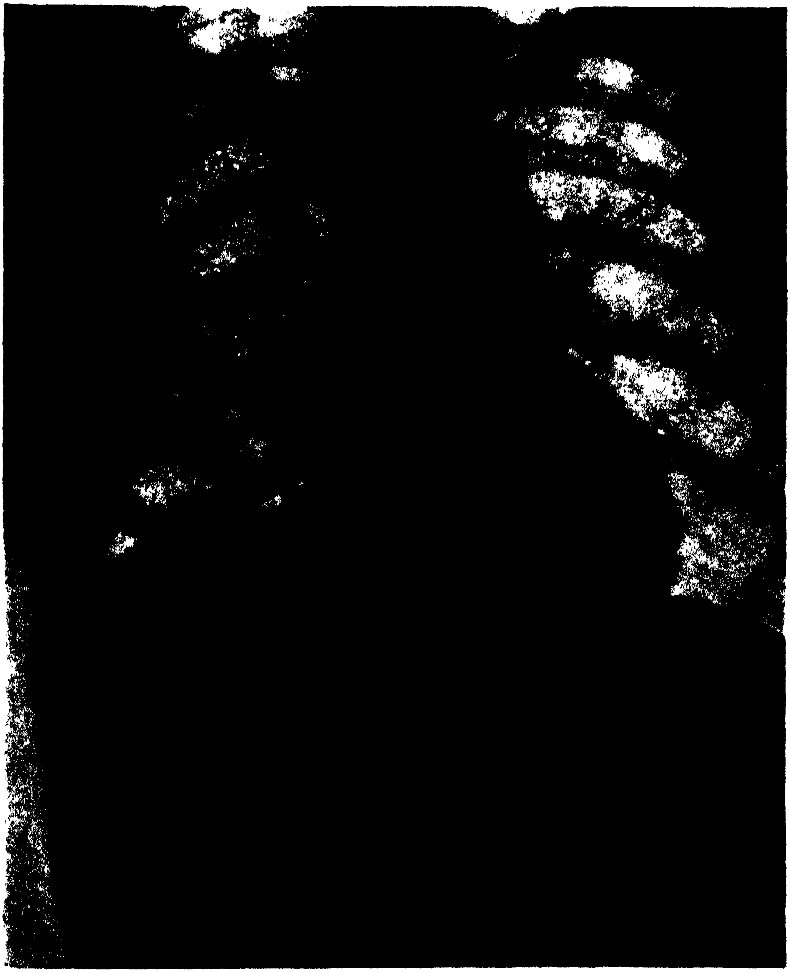


Fig. 72.—Multiple liver-abscesses from a case of acute amœbic dysentery, showing characteristic structure and zone of acute hyperæmia. Quarter nat. size.

Number, size, and situation of abscesses.—Liver abscess may be single or multiple. If multiple, there may be two, three, or many. When single, the abscess sometimes attains a great size. Frequently it is as large as a coco-nut, or even larger; the entire liver even, with the exception of a narrow zone of hepatic tissue, has been converted into a huge abscess sac. When multiple, the individual abscesses are generally smaller, ranging from the size of a filbert to that of an orange (Fig. 72).

As might be expected from considerations of the relative size of the parts, single abscess is much more common in the right than in the left smaller lobe. The upper part of the right lobe might be termed the seat of election.

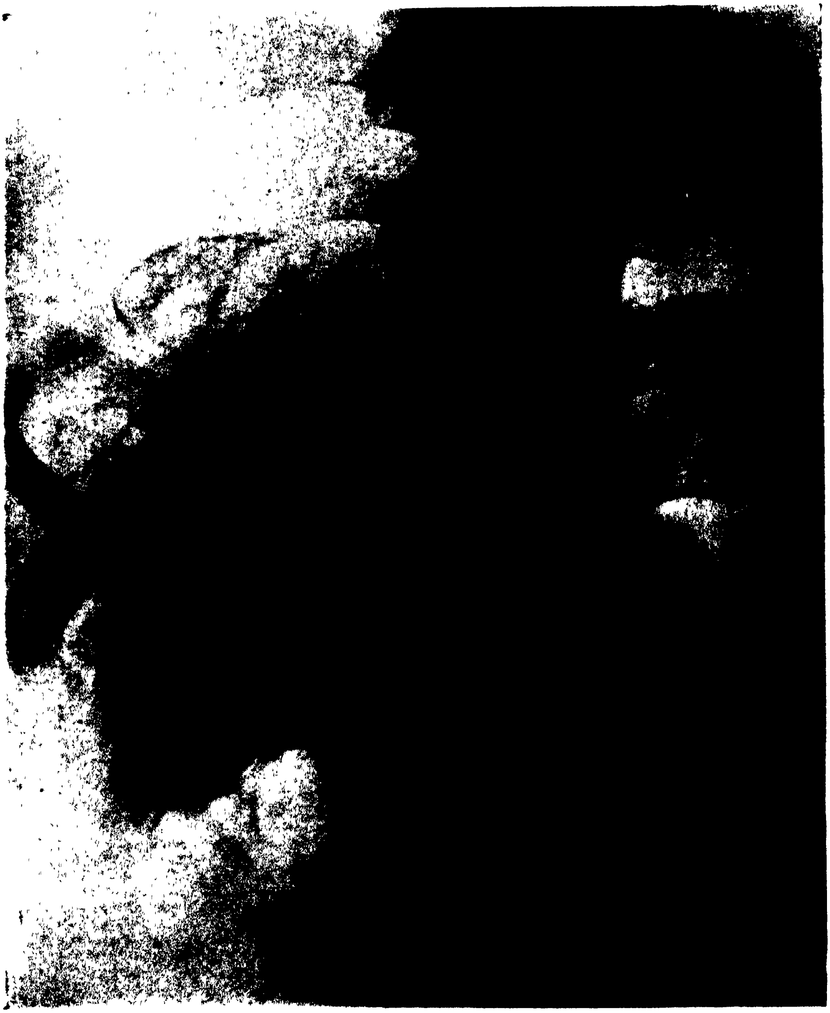


Radiograph of dome of diaphragm in liver abscess.

(Dr. Carmichael Low.)

LIVER ABSCESS.

PLATE XIV



Radiograph of cretified abscess in right lobe of liver.

(*Radiograph by Dr. M. Cordiner*)

LIVER ABSCESS.

PLATE XV

Compensatory hypertrophy of the left lobe is commonly produced if there is great destruction of the right.

Adhesions to surrounding organs are frequently, though not invariably, formed as the abscess approaches the surface of the liver. In this way the danger of intraperitoneal extravasation is usually averted.

Intestinal ulceration usually co-exists; it may be very extensive, or confined to a few small punched-out ulcers, generally in the neighbourhood of the cæcum. Or, again, there may be no visible lesions of the mucous surface.

Pulmonary inflammation and abscess from escape of liver pus into the lungs are sometimes discovered *post mortem*. Generally the pulmonary abscess communicates with the mother abscess in the liver by a small opening in the diaphragm, the pleural sac being shut off by adhesions. (Plate XVI.)

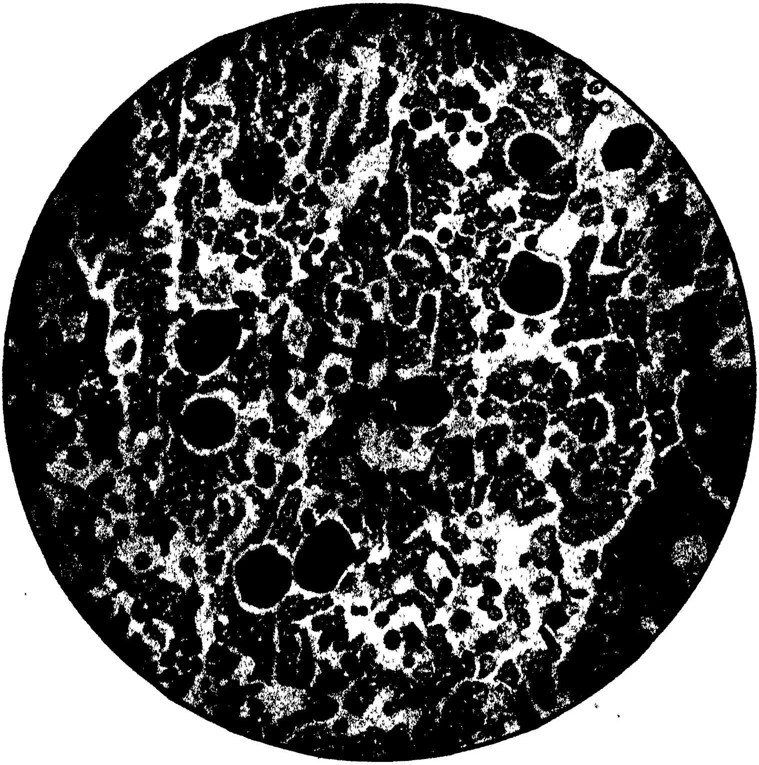


Fig. 73.—Microscopical section of liver abscess, showing *Entamœba* at margin of abscess cavity surrounded by necrotic liver cells.

Liver pus.—The naked-eye appearance of liver pus is peculiar, almost characteristic. When newly evacuated, it is usually chocolate-coloured, streaked, or mixed, with larger or smaller clots or streaks of blood, and here and there with streaks of clear mucoid yellowish material. It is so viscid that it will hardly soak into the dressings; it lies on the surface of the gauze like treacle on bread, spreading out between the skin and the dressing, and finding its way past the edge of the latter rather than penetrating it. When quite fresh, here and there little islands of what may be described as laudable pus may be made out in the brown mass. Sometimes it contains considerable pieces of necrotic tissue. Occasionally, also, from admixture of bile, the abscess contents are green-tinged; they are rarely offensive unless the abscess lies near the colon. Under the microscope many blood-corpuscles are seen, besides much broken-down liver tissue, large granular pigmented spherical cells, lecithin plaques, leucocytes, débris, oil globules, hæmatoidin, occasionally cholesterin, Charcot-Leyden crystals and sometimes a few entamœbæ. Cysts of *E. histolytica* are *never* found.

Entamœbæ and other organisms.—In Egypt, India, and elsewhere entamœbæ may be detected in half the cases. Usually they cannot be found in fresh liver pus, either aspirated or escaping during operation, but they appear, often in great profusion, four or five days later in discharges from the drainage-tube. They may occur in strings of eight to ten. Unless the patient is treated with emetine, the amœbæ may persist in the discharge until the abscess has healed. The Editor has succeeded in growing them on Drbohlav's selective medium when they were not apparent in the pus. The longer the abscess has persisted the larger its size, and the more difficult it is to find amœbæ (Fig. 73). The pus is bacteriologically sterile, but occasionally may become secondarily infected by *Bact. coli*, hæmolytic streptococci and *Bact. enteritidis.*

Encystment.—In rare instances liver abscess pus, instead of being chocolate-coloured and viscid, is yellow and creamy, particularly when the abscess becomes encysted. The walls are thick, smooth and fibrous. In the course of time the contents become cheesy, and ultimately cretified until the cyst shrivels up and contracts (*see* Plate XV). Calcified abscesses are occasionally found by radiography, and do not give rise to symptoms.

Bilaterality of the liver.—Until recently it was considered that no differences existed between the right and left branches of the portal vein, the hepatic artery and the hepatic ducts, although the right lobe of the liver is treble the size of the left. Cantlie in 1884 first noted hypertrophy of the left lobe of the liver consequent upon total destruction of the right. On this account, and also on account of the embryological development, it was suggested that the generally accepted anatomical division of the liver is incorrect and that it should be divided, not by the antero-posterior fissure, but by a line drawn from before backwards through the fundus of the gall-bladder to the spot where the anterior vena cava grooves the back of the liver; this is the mid-line of the liver. This view is borne out by pathological studies and the results of injection of the portal and hepatic veins and hepatic artery (McIndoe and Counseller). Copher and Dick (1928) demonstrated that the distribution of the portal streams in the liver of the dog can be determined by injections of trypan blue, and that there are at least three distinct and separate currents (streamline phenomena) in the portal vein. Hypertrophy of the left hepatic lobe ensues upon partial or complete destruction of the right, a feature of considerable importance in diagnosis.

The genesis of liver abscess.—Amœbic abscess of the liver appears to be the result of portal embolism from amœbic ulcers in the bowel. According to Rogers, the focus is usually in the right sector of the abdomen, either in the cæcum or ascending colon; this fact, therefore, accounts for the common situation of such an abscess in the right hepatic lobe. Direct infection of the anterior surface of the liver may possibly take place from an amœbic ulcer in the hepatic flexure, *via* the peritoneum, but there is no evidence to show that this constitutes the usual method. In *amœbic hepatitis*, which is probably the precursor of amœbic abscess, there appears to be a massive amœbic portal infection. Probably the great majority of the organisms are destroyed by resulting tissue-reaction; survivors multiply and cause necrosis of the surrounding liver cells and thus constitute the starting point of a liver abscess. Cytolysis is brought about by the rapidly multiplying amœbæ; but ultimately the amœbæ themselves are destroyed by the products of their own activity. Sterile amœbic abscesses at this stage are particularly liable to secondary infection with pyogenic organisms. As originally pointed out by Councilman and Lafleur, the primary lesion is central necrosis of the liver lobule, a prelude to subsequent abscess formation.

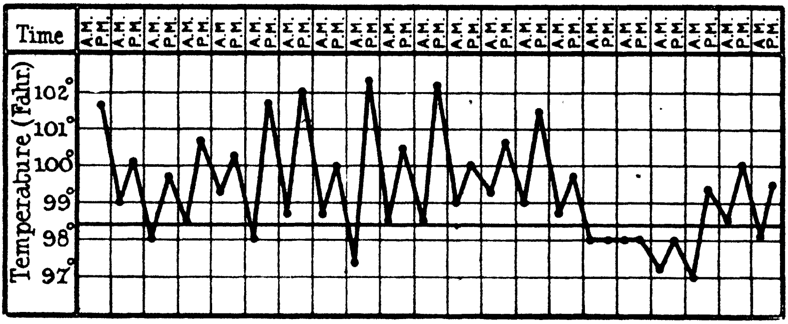


Chart 23.—Amœbic abscess of liver.

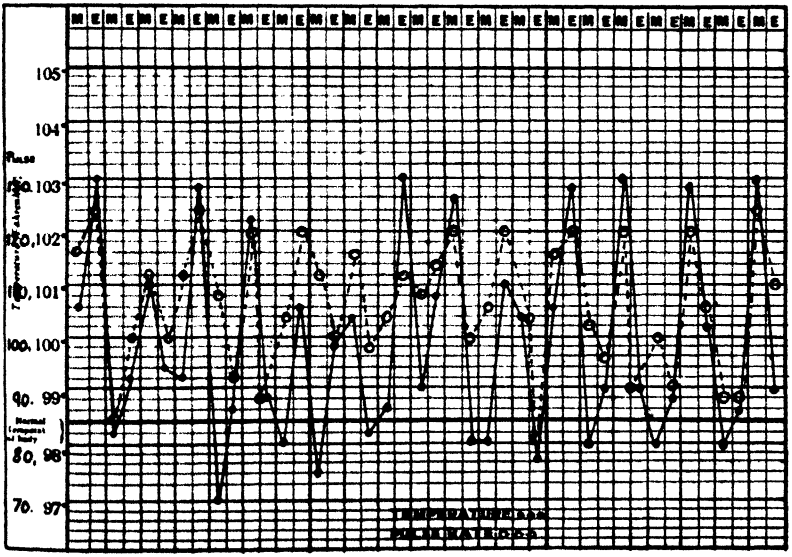


Chart 24.—Amœbic abscess of liver.

Hectic fever with tendency to tertian periodicity. Dotted line = pulse-rate.

Symptoms.—There is great variety in the symptoms of liver abscess. As a general rule, the patient is one who has long resided in the tropics and who may at some time or other have suffered from subacute attacks of dysentery. At first he becomes conscious of a sense of weight and fullness in the right hypochondrium, and later suffers from sharp stabbing pains over the hepatic area, accentuated by coughing.

Shoulder pain.—In a considerable proportion of cases a sensation of uneasiness or rheumatic pain around the right shoulder-joint is complained of, especially at night. Usually this is referred to the acromial region (appropriately termed, "the liver wing"). It is due to reflex irritation of the phrenic nerve, transmitted through the fourth cervical root from which the supra-acromial and supra-clavicular cutaneous nerves originate in the cervical plexus, and it is comparable to that of diaphragmatic pleurisy or gall-bladder disease. In left-lobe abscess pain is referred to the *left* shoulder-joint.

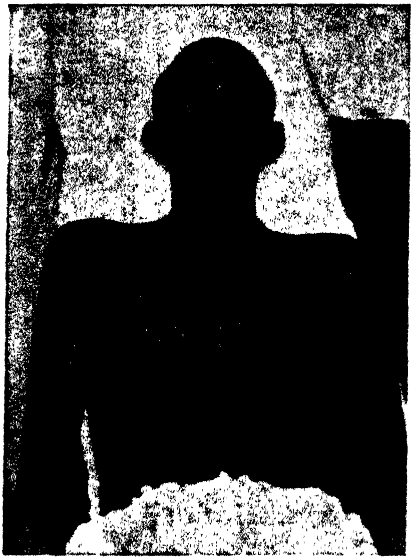


Fig. 74.—Clinical picture of liver abscess, showing enlargement of liver and bulging of chest wall.

General features.—Soon the patient becomes feverish, particularly towards evening, and may experience a few short rigors. He begins to lose flesh, and his complexion assumes a yellow, muddy tinge. A quotidian fever now becomes a regular feature, every evening reaching 102° F., and sinking to below normal in the morning (Charts 23, 24). The pyrexial bouts are accompanied by profuse sweats, necessitating frequent changing of clothing during the night. The patient is emaciated, his tongue furred, the extremities cold and clammy; breathing is shallow and mainly thoracic. Sometimes an actual swelling in the epigastrium may be observed over the site of the abscess. Discomfort or deep-seated pain may be produced by palpation and deep percussion over the right hypochondrium. The lower border of the liver is usually enlarged below the costal margin; sometimes, but less frequently, it extends upwards an inch above the normal, while posteriorly the dullness can be detected from the angle of the scapula to the costal margin. It may be further observed that the upper line of dullness is arched, and is altered by changes in position, when the patient lies on his left side or when he stands up. Deep inspiration may give rise to acute pain, and sometimes one or two tender points may be discovered in the lower intercostal spaces. The spleen is not enlarged. On auscultation, pleuritic rubs may be detected at the base of the right lung, or signs of compression, such as inspiratory crepitations, decreased breath-sounds, or diminution of vocal fremitus may be noted at the base of the right lung (Fig. 74). Pain is usually relieved by lying on the affected side (Fig. 75).

In abscess of the left lobe a tumour of variable outline, sometimes resembling in shape and position an enlarged spleen, may be felt in the epi- or hypogastrium. Usually there is some compression involvement of the base of the left lung, but it must be remembered that such a tumour may, arise from compensatory hypertrophy of the left lobe.

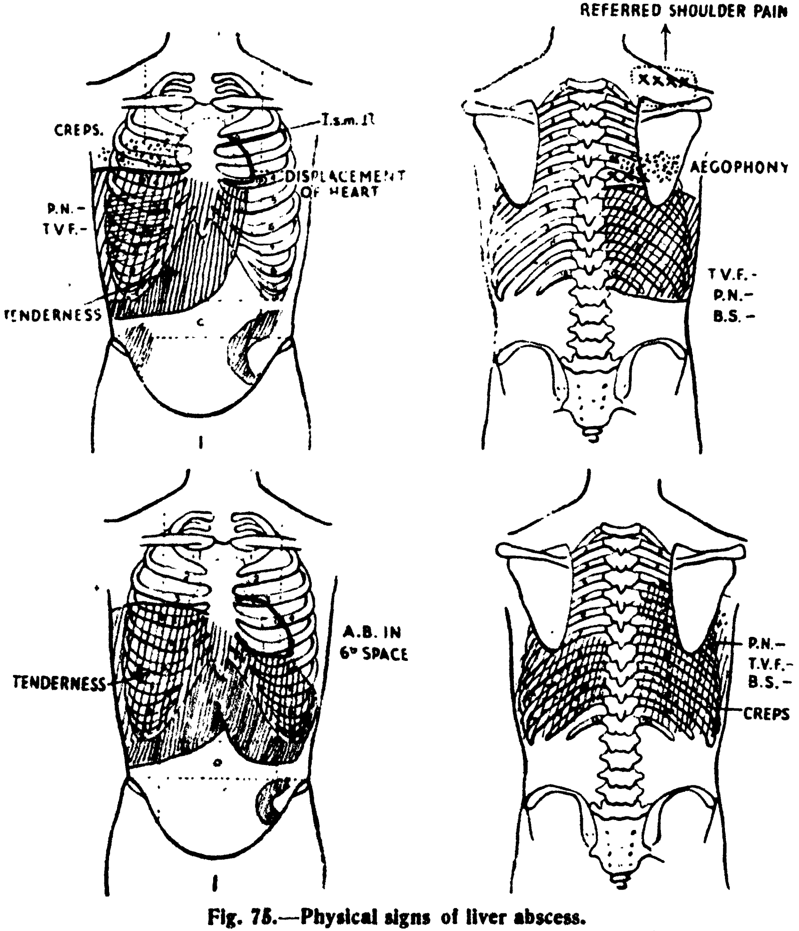


Fig. 75.—Physical signs of liver abscess.

Above—**Of right lobe of liver, cured by aspiration with Potain's aspirator** (6.7.25).

Leucocytes, 9,000 ; *E. histolytica* cysts in fæces. I s.m. II, basal systolic murmur ; P.N.—, percussion note diminished ; T.V.F.—, tactile vocal fremitus diminished ; B.S.—, breath-sounds absent ; CREPS., crepitations.

Below—**With hypertrophy of the left lobe, cured by aspiration of 65 ounces of sterile pus** (21.12.21).

Leucocytes, 12,000 ; *E. histolytica* cysts in fæces. A.B. apex-beat ; P.N.—, percussion note diminished ; T.V.F.—, tactile vocal fremitus diminished ; B.S.—, breath-sounds absent ; CREPS., crepitations.

As the case progresses, so the patient becomes more emaciated ; hectic with drenching nocturnal sweats continue ; liver dullness and increase ; or general enlargement may subside, and percussion reveal a local bulging in an upward or downward direction. If the abscess which has now formed is not relieved, the patient may die worn out after months of illness; or the abscess, having attained great dimensions, may burst into the right lung or pleura, or even elsewhere, and be discharged, with either recovery, or death from continued hectic fever and exhaustion or from some intercurrent complication. (Plate XVI.)

The blood shows a well-marked leucocytosis of 15,000–35,000, though in some rare cases there may be no appreciable rise. The mean average of the differential count in the Editor's series of cases is 70·8 per cent. polymorphonuclears; 22·2 per cent. lymphocytes; 6 per cent. large mononuclears; and 1 per cent. eosinophils. With liver abscess of long standing there is usually severe secondary anæmia, and occasionally the blood changes may assume features of the pernicious type.

In two exceptional cases of hepatic abscess recorded by the Editor the serum agglutinated *Bact. enteritidis* in high titre, with co-agglutination of *B. typhosum*, and the former organism was isolated from the abscess pus as well as from the fæces.

Great variety in the urgency of symptoms.—Although the foregoing is a fairly common history in liver abscess, there are many instances in which the initial symptoms are much more urgent and the disease progresses much more rapidly. In other instances subjective symptoms are almost entirely absent, or so subdued that the true nature of the case may be entirely misapprehended until the abscess bursts through the lung or bowel, or a fluctuating tumour appears in the neighbourhood of the liver; or, perhaps, until the unsuspected abscess is discovered on the post-mortem table.

Sometimes the initial fever is high, and persists for a considerable time, but later it usually becomes distinctly quotidian and intermittent; sometimes temperatures of 103° and 104° F. may be recorded. There is not one single cardinal sign which may not be absent in hepatic abscess; thus, large collections of pus have been noted unaccompanied by fever. Marked rigors are rare but, when present, indicate threatened rupture through the diaphragm cr into some viscus. Sweating accompanying the pyrexia usually takes place about the head and neck. Enlarged cervical and axillary glands on the affected side may sometimes be noted, while rheumatic-like pains in, or swellings around joints, and clubbing of fingers have been described. Pain of some description is rarely absent. Usually, a sense of fullness and weight in the region of the liver, or maybe referred to the infrascapular region, is complained of; stabbing and stitch-like pains may be increased by pressure, and especially by deep inspiration or coughing. Localized painful areas usually occur below the costal margin, and indicate that the abscess is pointing in that direction. Pain on swallowing, when the bolus traverses the lower end of the œsophagus, has been recorded. Pain on firm pressure with the finger-tips in an intercostal space, and over a limited area, is a common and valuable localizing sign. Shoulder pain, in about one-sixth of the cases, may be the only symptom and may be noted before the advent of fever.

Attention may also be drawn to the respiratory symptoms; a painful cough, possibly due to reflex irritation of the diaphragm, may be prominent,

Radiograph of liver abscess bursting through the diaphragm into base of right lung, whence the pus is being evacuated through a branch of the right bronchus. A—collection of pus in pleural cavity; B—valve-shaped opening through diaphragm at site of abscess in liver. (*Radiograph by Dr. M. Berry.*)

LIVER ABSCESS.

PLATE XVI

while the respiration may be rapid and shallow. The patient usually lies on his back, inclining slightly to the affected side; if the abscess is on the right, lying on the *left* side becomes distressing owing to adhesions, or possibly to pressure on the heart.

The tongue is generally furred, the digestion disturbed; flatulence and diarrhœa are frequent. There may, but infrequently, be concurrent amœbic dysentery with blood and mucus in the stools.

The heart may be displaced laterally or upwards by pressure of a large abscess. Tachycardia and cardiac irregularities may result from toxic absorption or from pressure.

Rigidity of the upper part of the right rectus muscle may be noted if the abscess is situated in the vicinity of the gall-bladder. Percussion, besides eliciting tenderness and causing pain, may convey to the examiner a sensation of *ballottement* as of percussing a thick-walled elastic bag filled with air. The right upper superficial reflex may be diminished or absent.

Swellings in the epi- or hypogastrium closely simulate intra-abdominal tumours, and in apyrexial cases of hepatic abscess their nature may not be suspected until they have been aspirated. There may be varicosity of the epigastric veins. Local *œdema* over one or more intercostal spaces is sometimes apparent; local *bulging* usually indicates the site at which the abscess is pointing (Fig. 74).

Friction rubs, pleuritic or peritoneal, may sometimes be found; while pneumonic signs at the base of the right lung indicate contiguity of the abscess to the diaphragm. Œdema of the feet occurs in advanced cases.

The urine may contain albumin as the result of chronic pus-absorption. When considerable destruction of hepatic substance has taken place, the amount of urea is diminished and that of ammonia increased.

Jaundice is not by any means common; when intense it may be caused by pressure of the abscess on the bile canaliculi, or even the common bile duct. Quite commonly, however, there is latent icterus with slight yellow tingeing of the conjunctivæ.

The abscess may rupture into any contiguous organ, thereby producing spontaneous cure; generally it ruptures into the lung or pleura. When into the *lung*, the abscess contents may be suddenly coughed up in mouthfuls of frothy pus and blood: but usually this process is much more gradual and a few drachms are coughed up at a time, but in favourable cases the amount of expectoration gradually diminishes. Amœbic abscess of the lung—resulting from trans-diaphragmatic rupture—is apt to be mistaken for pulmonary tuberculosis. Amœbæ are only exceptionally found in the expectorated pus, but usually striated muscular fibres from the diaphragm may be recognized.

Expectorated liver-pus is usually characteristic, being chocolate-brown and particularly viscid.

Arrest of the discharge may not necessarily indicate recovery though cessation of the cough may be followed by rise of temperature and reappearance of night-sweats. Alternate emptying and refilling of the abscess cavity may recur many times before final recovery. In some cases expectoration never ceases. and is accompanied by other signs of pulmonary absorption, such as respiratory distress and clubbed fingers. Sudden rupture is often accompanied by the passage of melænic stools.

Rupture into the *pleura* may lead to pleural effusions, which may simulate empyema. Aspiration of these cases may yield clear yellow and highly albuminous pleuritic fluid. Pneumothorax may sometimes ensue.

Hepatic abscess may rupture into the *stomach*, causing vomiting of pus ; into the *bowel*, causing diarrhœa and discharge of pus in the fæces ; or, with fatal results, into the *pericardium* or *peritoneum*. Pericarditis, from close contact with intrahepatic suppuration, has also been recorded.

Rupture into the gall-bladder, bile-ducts, hepatic veins, portal veins, inferior vena cava and pelvis of the right kidney have also been reported.

Finally, spontaneous rupture may take place through the abdominal wall, and the abscess, by tracking along the round ligament, may empty itself. The surrounding skin may thus become infected with amœbæ.

From a study of 50 cases of amœbic abscess under the Editor's care it has been possible to set out the following table :—

	No. of patients.
History of previous dysentery	30
Entamœba histolytica or cysts in fæces	23
Shoulder pain, right	22
„ „ left	3
Pyrexia, intermittent	39
„ remittent typhoid-like	4
„ sudden onset, with rigors	2
Pyrexia absent	7
Night-sweats	40
Dysenteric infiltration of bowel—	
Sigmoid flexure	12
Cæcum and sigmoid	4
Enlargement of liver, upwards	12
„ „ downwards	38
Pain and tenderness in liver	24
Displacement of heart	4
Associated signs at base of right lung	38
Pleuritic rub	6
Rupture of abscess into lung	6

Mortality.—Formerly the case-mortality was high, 50–80 per cent., but at the present day, ipecacuanha and emetine, recognition of the intimate connection of liver abscess with amœbic dysentery, and improved methods for the evacuation of pus, have brought the mortality-rate to practically nothing. Death may be due to pressure on the abscess, to rupture and gangrene of the abscess-wall, to pneumothorax, to pneumonia, to associated dysentery, or to other intercurrent disease. Recovery may follow encystment or, possibly, absorption of the abscess.

Diagnosis.—Of all the grave tropical diseases, none is so frequently overlooked as abscess of the liver. Acute sthenic cases are readily enough recognized ; not so insidious asthenic cases.

The most common mistakes in diagnosis are : (1) Failure to recognize the presence of disease of any description, even when an enormous abscess occupies the liver. (2) Misinterpretation of the significance and nature of a basal pneumonia—a condition often accompanying suppurative hepatitis. (3) Attributing the fever symptomatic of liver abscess to malaria. (4) Mistaking other diseases for abscess of the liver, and *vice versa*—for example, non-suppurative hepatitis, such as that attending malaria subtertian ; suppurative hepatitis before the formation of abscess ; syphilitic disease of the liver—softening gummata which are often attended with hectic fever ; pylephlebitis : suppurating hydatid ; suppurating actinomycosis ; gall-stone and inflammation of the gall-bladder ; subphrenic abscess due to ruptured gastric or duodenal ulcer, or appendix abscess ; abscess of the abdominal or thoracic wall ; pleurisy ; encysted empyema ; pyelitis of the right kidney ; bilharziasis ; scurvy and similar blood-diseases associated with hepatic enlargement ; ulcerative endocarditis ; kala-azar ; undulant fever ; trypanosomiasis, tuberculosis, and malignant disease. Any of these may be attended with fever of a hectic type, increased area of hepatic percussion dullness, and pain in or about the liver.

Differential diagnosis from suppurative cholecystitis without the aid of a " shadowcol " examination may be particularly difficult.

Cantlie originally classified pus in the neighbourhood of the liver into :—

(1) Suprahepatic abscess ;
(2) Intrahepatic abscess ;
(3) Infrahepatic or subhepatic abscess.

Suprahepatic abscess is not synonymous with " subdiaphragmatic abscess ; " it means the formation of pus between the layers of the broad ligament of the liver.

Frequently, a correct diagnosis can be reached only by repeated and careful study of the case in all its aspects. Golden rules in tropical practice are to think of hepatic abscess in all cases of progressive deterioration of health ; and to suspect it in all obscure abdominal cases associated with evening rise of temperature, particularly if there be an upward enlargement of or pain in the liver, leucocytosis, and a history of dysentery—not necessarily recent.

Low pneumonia of the right base in a tropical patient should always be regarded with suspicion, for it may mean abscess of the subjacent liver.

Perhaps the most common error is to regard the hectic fever of liver abscess as attributable to *malaria*. The regularity with which the daily fevers recur, the daily chilliness, or even rigor, coming on about the same hour, the profuse sweating, and other circumstances so compatible with a diagnosis of malaria, all contribute to this mistake. So common is the error that Osler declared he hardly ever met a case of liver abscess which had not been drenched with quinine. The periodicity of fever, and a polymorphonuclear leucocytosis should obviate so serious an error.

To mistake other forms of suppuration for liver abscess is not so serious, because in many suppurative diseases the treatment is the same as for liver abscess, and no bad result need follow if diagnosis is not quite accurate.

Intrahepatic suppuration may supervene in ascaris infection, in melioidosis (p. 282), in ascending pylephlebitis secondary to appendix abscess, in diverticulitis and, rarely, in infections with hæmolytic *Staphylococcus* *s*, or very exceptionally with bacillary dysentery. Suppurating abscesses have been reported secondary to duodenal ulceration and enteric infections. Carcinomatosis of the liver, unaccompanied by jaundice, may simulate amœbic abscess. A right perinephritic abscess may have to be considered. In subdiaphragmatic abscess caused by perforation of a-gastric or duodenal ulcer, an abdominal swelling can usually be recognized occupying a triangular area on the affected side. Gas is usually present and can be recognized by a resonance in the upper part which serves to distinguish it from liver abscess.

Pancreatic cyst elevating the left (less often the right) lobe of the liver may imitate an abscess, but it is not necessarily accompanied by fever.

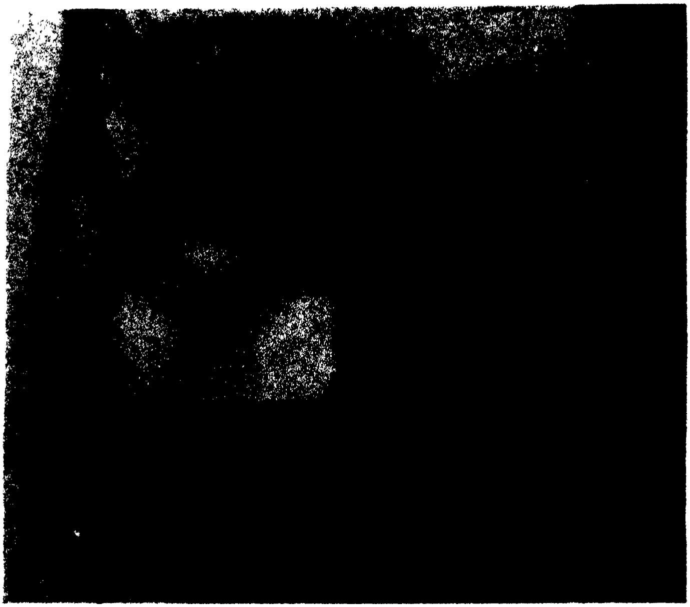


Fig. 76.—Visualization of amœbic liver abscess by puncture and injection of lipiodol in erect position. (*After* Snapper, "Chinese Lessons to Western Medicine.")

As a rule, it forms a definite tumour of considerable size in the left hypochondrium. Solitary non-parasitic cysts of the liver or polycystic disease may also have to be considered. Phantom tumour may give rise to difficulty, but this gradually disappears under a general anæsthetic.

A serious error is to overlook the presence of leucocythæmia, kala-azar pernicious anæmia or scurvy, and to proceed to aspirate an enlarged liver on the supposition that the symptoms arise from abscess.

Amœbic abscess of the liver which has ruptured through the diaphragm may have to be differentiated from many other pulmonary conditions, such as broncho-pneumonia, tuberculosis, actinomycosis, and malignant disease of the lung.

The presence of *Entamœba histolytica* cysts in the fæces is suggestive but by no means conclusive, of amœbic abscess. They are usually found in about 45 per cent. of all cases. Occasionally they may be cultured from the fæces in cases in which they are not visible under the microscope.

X-ray examination may confirm the upward enlargement in the liver, and bulging and " tenting " of the right dome of the diaphragm. Screening usually shows that it does not move on respiration (Plate XIV). Should, however, the abscess be situated in the centre of the liver, even if of considerable size, no definite information is usually obtainable by radiography except when the abscess has become partially encysted or calcified (Plate XV), when the outlines become apparent by X-ray. Occasionally, however, the outline of the liver abscess may show up as a more opaque area in the liver substance affording exact location for the exploring syringe. Occasionally, too, especially after inspiration, air, or possibly oxygen, appears in the abscess cavity and shows up the fluid level. Injection of air through the aspirating syringe has been practised with success, while lipiodol injection facilitates visualization (Fig. 76). The outline of the diaphragm is blurred when the abscess is near the upper surface of the liver. Normally the upper margin of the hepatic shadow forms a right angle with that of the vertebral column, but when abscess is present this may become more acute.

The bromsulphalein test, as an indication of hepatic disease and liver abscess has so far proved disappointing. The lævulose tolerance test is more satisfactory, especially if taken in association with decrease of plasma proteins and response of hypothrombinæmia to injections of vitamin K.

Diagnostic aspiration.—To make the diagnosis of liver abscess certain, aspiration must be performed. When the needle enters the liver, an up-and-down pendulum-like movement will be communicated to its outer extremity, in harmony with the rising and falling of the organ in respiration. If the needle does not exhibit this movement, its point may be in an abscess cavity, but such an abscess is not in the liver.

Prognosis.—The prognosis in early operations on single abscess of the liver, provided there is no dysentery or other complication, is good. In multiple abscess, or in single abscess, if there is active dysentery or other serious complication, the prognosis is bad ; if there are more than two or three abscesses, it is usually hopeless.

The *question of return to the tropics* after recovery from liver abscess frequently crops up. If feasible, and if the patient has not to make too great a sacrifice, he ought to remain in a temperate and healthy climate. There are many instances, however, of individuals who have enjoyed permanent good health in the tropics after recovery from liver abscess. Before return the bowel should be thoroughly cleansed of amœbic infection. Neglect of this precaution may lead to reinfection and recurrence seven years after the formation of the first abscess.

Treatment.—Hepatitis which has not proceeded to abscess-formation should be treated, especially if dysentery be present or has been antecedent, with full doses of emetine, repeated once or twice a day for two or three days or longer, by a cautious use of the purgative sulphates, and with poultices, rest, and low diet (*see* p. 502). Emetine should be injected in 1 gr. doses up to a total of 12 gr., and if cysts of *E. histolytica* are present in the stools, by a combined course of E.B.I. and quinoxyl. If there be much pain, relief may be afforded by either wet- or dry-cupping over the liver, or by leeches. Ammonium chloride, 20 gr. doses, three times daily, is commonly prescribed.

When rigor, or hectic fever, or local bulging, or persistent fever and local symptoms give ground for suspecting that abscess has formed, active medication must be suspended, and measures taken without unnecessary delay to locate the position of the pus by the aspirator.

Preliminary aspiration.—When he uses the aspirator the surgeon must be prepared to continue until all the pus is evacuated, or under exceptional circumstances, to operate.

Deep cocaine anæsthesia usually suffices, but nervous subjects should have gas and oxygen. A medium- or full-sized aspirator needle should be used, as the pus, owing to its viscidity, may not flow through a cannula of small bore.

If there are localizing signs, such as a tender spot, a fixed pain, localized œdema, localized pneumonic crepitus, pleuritic or peritoneal friction, these should be taken as indicating, with some probability, the seat of the abscess and the most promising spot for exploratory puncture. If none of these localizing signs is present, then, considering the fact that the majority of liver abscesses are situated in the upper and back part of the right lobe, the needle should, in the first instance, be inserted in the anterior axillary line in the 8th or 9th interspace. The needle should not be inserted more than 3¾ in. The distance of the inferior vena cava from any part of the chest wall is 4 in. The needle swings when the liver is engaged and, as it swings, it should be pushed gently forwards. The operator knows he is in the abscess cavity, because the needle is felt to pass into space. The syringe should then be affixed and aspiration commenced. Effusion of serum into the pleural cavity immediately adjacent to the liver abscess sometimes occurs.

In cases with cardiac or pulmonary embarrassment, aspiration can be efficiently carried out under local infiltration of skin and muscles with 2 per cent. novocain, to which is added 1 in 1000 adrenalin in the proportion of 10 drops to the ounce. The passage of the needle through the liver substance is painless. Should, however, the abscess point into the abdominal cavity, a general anæsthetic is advisable, for an open operation may become necessary. Occasionally the pus proves to be so thick that complete evacuation takes an hour or more; in these circumstances eusol in saline (half-strength) should be injected into the abscess cavity to dilute the pus.

An after course of combined emetine-bismuth-iodide and quinoxyl should be given to eradicate the amœbic infection from the bowel.

Open operations.—The indications for open operation are:—

(1) When after repeated aspiration no pus is obtained, but indications of its presence are too strong to be ignored.

(2) When an abscess points in the epigastrium, *i.e.*, is situated in the left lobe of the liver.

(3) When there is a large amount of pus which has been secondarily infected and has not yielded to treatment by aspiration.

The route for opening the thoracic or abdominal wall varies according to circumstances as follows :—

Transperitoneal route.—When pus is struck below the costal margin, the aspirator needle is left *in situ* and the abdomen is incised for a length of 3 in. (Kocher's incision), the intestines being guarded with packing. If adhesions are present, a sinus forceps is directed along the needle and pushed through into the abscess, and the blades are opened after withdrawal of the needle. The finger should be inserted into the abscess cavity. When the first gush of pus ceases, the exit is lightly plugged with gauze, the margins of the liver wound are carefully sutured to those of the parietal peritoneum, and the remainder of the wound closed. The gauze plug is now removed, and a wide drainage-tube, provided with a flange and lateral openings, is introduced to the bottom of the abscess cavity. Some surgeons use a wide-bore drainage tube, such as Tudor-Edwards empyema tube drain, pushed right to the bottom of the cavity to prevent extravasation.

Transpleural route.—Should the abscess be struck through an intercostal space, a couple of inches of (the 8th and 9th) ribs had better be resected. The diaphragm should then be stitched to the thoracic wall, or, better, to the skin as well, when the abscess may be opened with a forceps. An attempt should be made to stitch the capsule of the liver to the diaphragm. Should the pleura be opened, pneumothorax will result, but this is not necessarily serious. On no account should pus be permitted to enter the pleural cavity.

Sometimes it is simpler to expose the ribs and denude them of tissues. An iodine gauze pack should be inserted underneath the ribs and left for 3 to 4 days. Artificial adhesions are formed in the costophrenic sinus by a process of aseptic inflammation. Shears are then used to resect the ribs. Post-operative drainage is ensured by sinus forceps and a wide-bore tube. Dakin's solution may be used to irrigate as it exerts a solvent action on the liver abscess wall.

Treatment after operation.—For the first two days after a liver abscess has been opened the discharge is considerable, and the dressing may have to be changed frequently. Very soon, however, should the case do well, the discharge rapidly diminishes, and the dressing requires renewal only every other day, or every three or four days. During the first week the drainage-tube, provided it be acting efficiently, should not be disturbed, more particularly as it may be difficult to replace. Later, it may be removed and cleaned, and, when discharge has practically ceased, cautiously shortened. *It is a great mistake to begin shortening the tube before it is being pushed out, or so long as there is any appreciable discharge.* If there is the slightest indication, such as rise of temperature, that pus is being retained, the drainage must be rectified and the sinus, if necessary, dilated with forceps and finger, and a full-sized drainage-tube introduced as far as it will go. If this does not suffice, a counter-opening may have to be made. *Delay in remedying imperfect drainage is a serious—it may be fatal—error.*

Should an abscess be found septic, or should it become so, it must be flushed out daily, or twice a day, with a weak non-mercurial antiseptic, and a counter-opening made if necessary. Continuous drainage by the Carrel-Dakin tube method and daily eusol irrigation are often very successful. Where there is a thick necrotic zone delimiting the abscess, this continuous irrigation is highly necessary, and in order to dissolve the thick pus the injection of a ferment—enzymol (Fairchild) in the strength of 1 drachm to the ounce of water—is useful.

After a liver abscess has been opened and is draining well, temperature rapidly falls, and in a few days, or almost at once, becomes normal. Should fever persist, it is to be inferred either that the drainage is inefficient, or that there are more abscesses in the liver, or that there is some complication. If another abscess is suspected, it should be sought with the aspirator and, if found, drained.

It is advisable to give emetine in 1 gr. doses hypodermically, both before and after operation, and continue it for a fortnight, whichever operation is employed.

Discussion of the recognized methods of treatment of liver abscess.—The question is frequently and very reasonably asked why so many methods of treatment, medical as well as surgical, are employed in the treatment of liver abscess, and why some abscesses respond to injections of emetine while others are in no wise influenced by this drug. The answer appears to the Editor to be moderately simple. Aspiration of the abscess cavity by Potain's aspirator is the safest and most easily executed method. Sometimes more than one aspiration has to be carried out and an electric sucker may have to be employed. In the Editor's experience 28 per cent. of cases diagnosed as hepatic abscess resolve with emetine-therapy (12 gr.) followed by the E.B.I. and quinoxyl combined treatment. In these, probably, the formation of pus has not been extensive and the amœbæ are still active in the liver tissue. In 47 per cent., aspiration with Potain's aspirator, combined with emetine treatment, is successful. There still remains a proportion of cases (25 per cent.) in which open operation has to be resorted to, and emetine therapy has no appreciable effect whatever. These are the cases where either a large amount of pus is present or it is secondarily infected with streptococci or other organisms. It is disappointing to have to record that previous treatment of intestinal amœbiasis with E.B.I. and quinoxyl does not always prevent subsequent development of hepatic abscess.

Treatment of abscess discharging through the lung.—If an abscess is discharging through the lung and, although emetine has been freely administered, is not progressing favourably, the question of more efficient drainage by surgical means must be considered. There are two possibilities which render interference desirable: (*a*) Continued discharge of pus and blood, with or without attendant hectic fever—a condition which, if it persist, will, in all probability, in the end, kill the patient. (*b*) Not infrequently, prolonged discharge through the lung may induce fibrotic changes, pneumonia, or abscess with all its attendant dangers, such as thrombosis or abscess of the brain. (Plate XVI.)

In all cases of abscess discharging through the lung a careful register should be kept of three things—body-temperature, daily amount and character of expectoration, and, once a week, the weight. If temperature keeps up, if the amount of pus continues the same or increases, or if the patient continues to lose weight, an attempt should be made at all risks to reach and drain the abscess from the outside. If temperature remains normal, if pus gradually or intermittently decreases, and if the body-weight if maintained or increases, operation is unnecessary, or, at all events, should be deferred.

Medical treatment with full doses of ipecacuanha and emetine, maintained over a long period, generally exerts an almost miraculous effect and renders operative interference unnecessary.

In exploring the liver in such cases, it must be borne in mind that most likely the abscess cavity is collapsed, and that the sides of the abscess may be in contact. Such an abscess is not likely to be discovered unless the needle be thrust into its full extent and, whilst a good vacuum is being maintained in the aspirator, slowly withdrawn. If by good fortune the abscess has been traversed, then, when the end of the needle is crossing the cavity, a small amount of pus will be seen to flow.

Treatment of abscess rupturing into a serous cavity.—When there is evidence that an abscess of the liver has ruptured into the peritoneum, into the pleura, or into the pericardium, the particular serous cavity involved must be opened and at once treated on general surgical principles ; otherwise the patient will almost surely die. In the circumstances the surgeon will be justified in assuming great risks.

2. AMŒBIC ABSCESS OF THE BRAIN, SPLEEN AND EPIDIDYMIS

According to Armitage, 48 cases of amœbic abscess of the brain have been recorded, for the most part from Egypt. Like hepatic abscess, it is more common in men than in women. It is generally solitary, and may be regarded as a metastasis of hepatic abscess. The pressure symptoms resemble those of a cerebral tumour, and the abscess is invariably fatal. Amœbic abscess of the spleen was recorded by Rogers and others *post mortem*. Abscess of the epididymis was reported from China (Warthin).

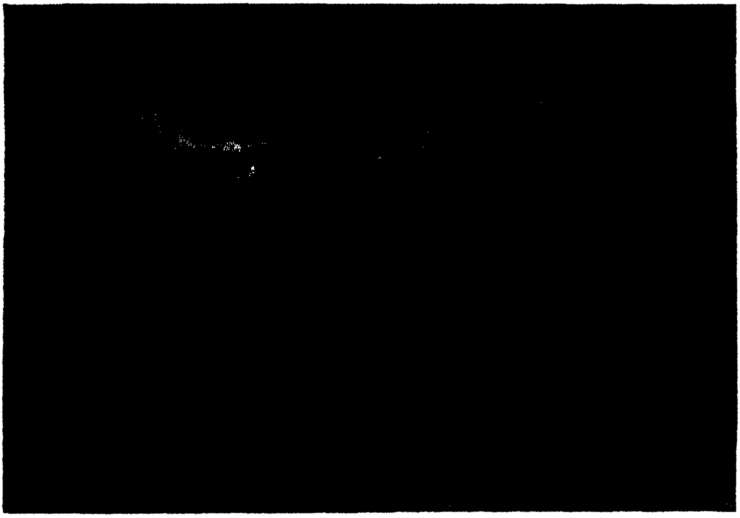


Fig. 77.—Amœbic granuloma and ulceration of abdominal parietes surrounding colostomy.

3. AMŒBIC INFECTION OF THE SKIN AND SUBCUTANEOUS TISSUES

Since 1892, it has been known that the skin may be subject to amœbic invasion in the vicinity of a discharging liver-abscess sinus. Amœbæ have been demonstrated in sections of the skin, and they are susceptible to emetine. Gangrenous lesions of the abdominal wall and perineum have been described from time to time, especially by Engman and Meleney (1931), while Hsu, in China, described a series of fourteen cases and showed that the condition is by no means rare. The Editor treated one such case, in which the parietes in the vicinity of a colostomy and the abdominal wall were involved (Fig. 77), with discharge of fœtid anchovy sauce pus. The patient was proved to have active amœbic dysentery. Extensive gangrenous destruction of the buttocks and skin of the back was seen in St. Mark's Hospital, London, in an ex-soldier who had served in India fifteen years previously; though he had never suffered from clinical dysentery, *E. histolytica* cysts were present in the fæces. The lower part of the rectum, the pelvic floor and the perineal tissues had been destroyed. Response to emetine therapy was quite remarkable. (Fig. 78).

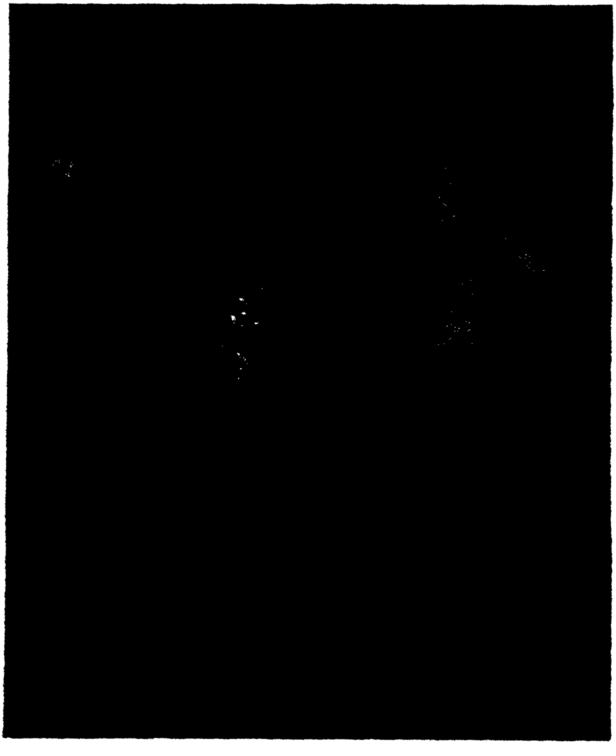


Fig. 78.—Amœbic ulceration of skin. Ulceration of sacrum, coccyx and perineum. (*W. B. Gabriel. Trans., Roy. Soc. Trop. Med. J.* 1933, 32 223.)

Amœbiasis cutis is a secondary infection of papillomata around the anus. The lesions have a punched-out appearance, and resemble in this respect intestinal amœbic lesions.

4. URINARY

A number of uncritical papers have appeared describing as amœbæ [illegible] prostatic or other inflammatory cells which may be present in subacute cystitis or prostatitis. When *E. histolytica* in vegetative form is present in the urine it comes through a fistula between the bladder and the ulcerated rectum, as in the case reported by Craig (1911). Amœbic ulceration of the urethra in the male, as well as of the cervix uteri in the female, has been reported by Hsu in China, and amœbæ have been demonstrated in the tissues in microscopic sections; *E. histolytica* in the urine may be derived from this source.

5. PULMONARY AMŒBIASIS

This type of case is distinct from pulmonary abscess secondary to that of the liver where infection of the lung tissue results from direct extension of the hepatic abscess or by rupture into the bronchus.

In primary pulmonary amœbiasis the amœbæ reach the lung by direct embolism from the bowel. Having gained the pulmonary circulation, they form firm nodules, which later break down into small abscesses. The symptoms produced closely resemble those of a fugitive broncho-pneumonia, or some form of tuberculous infiltration.

These patients, who have been at some time the subjects of amœbic infection, suffer from pulmonary symptoms, with profuse purulent expectoration, sometimes tinged with blood, and respiratory distress with intermittent pyrexia. They are apt, however, to have rigors, which may serve to differentiate the condition from other respiratory diseases. The physical signs vary, but are usually those of broncho-pneumonic consolidation, detectable at the border of the scapula, especially on the right side. Skiagraphy may be of little avail in diagnosis. Amœbæ are not found in the sputum. There is, as a rule, a distinct leucocytosis. The response to emetine treatment is rapid and almost diagnostic (Chart 25). A full course of injections should be given.

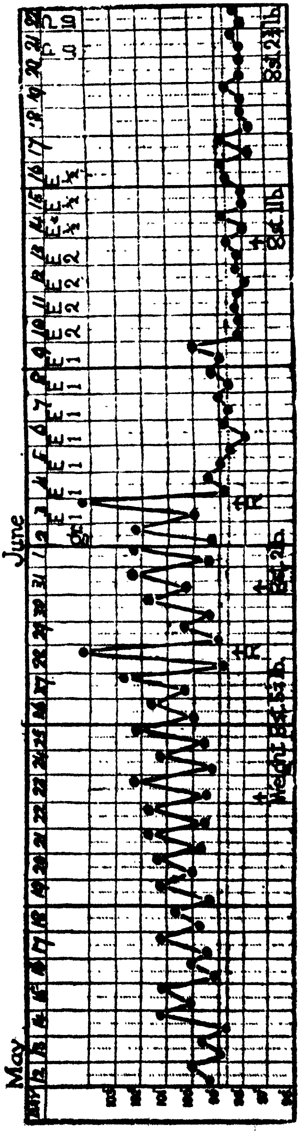


Chart 25.—Pulmonary amœbiasis with broncho-pneumonic symptoms and signs. Immediate improvement after institution of emetine treatment. (*Reproduced from "The Lancet."*)

BALANTIDIAL DYSENTERY

The occasional occurrence of *Balantidium coli* in the fæces, particularly in association with dysenteric diarrhœa, has been recognized for the last fifty years. It is only since Strong and Musgrave called attention to this subject that

Balantidium coli has come to be regarded as the germ cause of a particular type of colitis resembling in many respects amœbic dysentery. The parasite has been studied from the zoological standpoint, more especially in temperate climates, but it seems probable that extended observations will show that it is equally if not more prevalent in warm climates. It is a common parasite of the pig, and produces a fatal form of dysentery in monkeys in captivity and especially chimpanzees. Human cases have been reported all over the world, but especially from Germany and France, in those who tend domestic pigs. It is thought that cysts are transferred from the hands to the mouth during the handling of the intestines of infected animals. Mackenzie and Bean (1938) recorded the first case in England in a mental patient, and a second has been described.

How it attains the human intestine is not known, but as it is a common parasite of the pig, these animals should be regarded as the usual source of infection. Balantidium may live for a considerable time in water or fæces (one hour to three days). In liquid stools it exhibits great activity, indulging in locomotive as well as in rotary movements. For further description, *see* p. 877.

Geographical distribution.—Balantidiasis in man has been recorded from Russia, Scandinavia, Finland, Germany, France, Austria, Holland, Italy, Spain, Siberia, China (Tsingtau), Georgia, the Philippines, Cochin China, Andaman Islands, Sandwich Islands, Egypt, and the Sudan. Cases have also been reported from North America, North and South Carolina, Brazil, Porto Rico, Cuba and England.

Pathology.—There is little or nothing to distinguish the gross as well as the microscopic pathology from that of amœbic ulceration. The organisms have been found by Strong, Martini and Walker in the mesenteric glands. In thirty autopsies a variety of dysenteric lesions, from catarrhal congestion and diphtheritic patches to extensive ulceration, have been described. On section, Strong demonstrated the balantidium, not only in exudates on the surface of the bowel, but congregated in large numbers in the follicles, or embedded in the tissues forming the base of the ulcerations, including the submucosa and muscular coats, and even in the lumen of blood-vessels and lymphatics. The early lesions are minute hæmorrhages; later, ulceration and abscesses appear. Bowman stated that the colon throughout its whole extent may be a mass of ulcers from which hang shreds of necrotic tissue—lesions resembling those of amœbic dysentery.

Symptoms.—These are, in the present state of knowledge, indistinguishable from those of amœbic dysentery. The disease is chronic, its special nature being discoverable only on microscopic examination of the stools. Generally, only one or two balantidia are found, but as many as twenty may be seen in every field of the microscope. The blood usually shows no change; there is no leucocytosis and the polymorphonuclears represent 70 per cent. The ulcerations in the bowel, revealed by sigmoidoscopy, resemble those of intestinal amœbiasis as described by Mazza, Alvarado and Schürmann (1932). The mortality in 111 collected by Strong was 29 per cent.

Treatment.—Walker found that organic compounds of silver are effective in eradicating the infection. Thymol has been recommended, and oil of chenopodium, as in ancylostomiasis, has been reported to be successful. Young and Burrow (1943) cured seven cases with carbasone, 0·25 grm. twice daily for 10 days. This should be repeated if there is relapse. Yered tried a new remedy—carobinase—a watery extract of *Jacaranda decurrens*, 25 grm. in 500 c.c. of hot water, which is given as rectal lavage for three weeks. Methylene blue enemata, 2 pints of a 1 per cent. solution, are claimed to give good results. Westphal praises *Acranil*—hydrochlorate of acridine.

III. HELMINTHIC DYSENTERIES

Bilharzial dysentery.—Adeno-papillomata or ulcerations of the large intestine evoked by passage of eggs through the intestinal wall, are found in *Bilharzia mansoni*, *B. japonica*, and exceptionally in *B. hæmatobia* infections. The dysentery thus produced is met in those countries in which the parasites occur.

The stools contain yellow or bile-stained mucus with clots or streaks of blood, in which the bilharzia eggs can be found under a low power of the microscope. Eosinophilia associated with symptoms of dysentery is highly suggestive, and diagnosis should, if possible, be confirmed by the discovery of the characteristic eggs in the fæces. Sigmoidoscopic examination should help in doubtful cases. Pathologists should bear in mind that eggs are more easily found in the outer zone of solid fæces than in more central portions. Usually, pus cells in the fæces show a high proportion of eosinophils.

Infection with Œsophagostomum apiostomum and O. stephanostomum (p. 914).—These are rare intestinal parasites of man in Brazil, Northern Nigeria and Central Africa. When numerous they may give rise to dysenteric symptoms. The adult worms encyst under the submucosa, and may, together with their eggs, be recognized in the dysenteric discharges.

Infection with other helminthic parasites.—Chronic diarrhœa and possibly dysenteric attacks have occasionally been noted in intestinal infections with *Fasciolopsis buskii* (p 879), *Paragonimus westermanii* (p. 884), *Heterophyes heterophyes* (p. 883), and *Strongyloides stercoralis* (p. 917).

DIFFERENTIAL DIAGNOSIS OF THE DYSENTERIES

Mixed infections of different forms of dysentery may, of course, occur in those countries in which these diseases are endemic.

Combined infections of amœbic and bacillary dysentery are the most frequent. Such cases do not usually occur in temperate countries but during the course of severe epidemics of bacillary dysentery, when bacillary infection may be grafted upon some long-standing amœbic ulceration of the bowel. On the other hand, this dysentery may be followed by amœbic invasion of the bowel, which makes diagnosis still more difficult.

Bacillary dysentery occurs quite commonly as a terminal event in intestinal bilharziasis, and amœbic ulcers may sometimes be associated with the same condition.

Giardiasis.[1]—Of the intestinal flagellates which appear in the fæces, perhaps *Giardia* (*Lamblia*) *intestinalis* has the best claim to be regarded as pathogenic. The usual habitat of the parasite is in the upper part of the small intestine, but it may also heavily infest the duodenum. When newly passed in the fæces it is very active, presenting a characteristic appearance. During the passive stages cysts appear in the fæces in enormous numbers, and may be associated with those of *E. histolytica*. They are generally found in 4–16 per cent. of normal natives of the tropics. Other species are found in mammals and in reptiles, and one in the mouse, *Giardia muris*, is closely allied to the human parasite. In children in Northern countries giardia infection is three times as common as in adults. (In America 48·1 per cent. of industrial school children.) For a description of *G. intestinalis*, *see* p. 875.

---

[1] Giardiasis or lambliasis is mentioned in this section for the sake of completeness, although the diarrhœa associated with the parasite cannot strictly be classified as a dysentery.

In England and in Canada the parasite has been found in the intestine of quite a large number of normal children, while Boyd, Silverman, and others have shown that it can occasionally be demonstrated in the duodenal juice, bile, and gastric contents.

Some regard this parasite as pathogenic on the grounds that it is found in large numbers when the stools are liquid, and that quantities of mucus are passed containing active parasites.

Giardia infection is associated at times with a type of recurring diarrhœa accompanied by abdominal discomfort. The stools may be of a peculiar clay colour and pultaceous consistence, and may resemble those of sprue, or in English children of cœliac disease (R. Miller, 1926). Fat absorption has been found defective and excretion of bile below normal; both are attributed to mechanical effects of these parasites on the intestine. After these attacks, the encysted forms of *G. intestinalis* are present in large numbers in the fæces. Relapses tend to occur periodically, but eventually tolerance is acquired. Flatulence is almost invariable. In the acute stage the abdomen is tender and there is general discomfort. Véghelyi, who made observations on children in Budapest, described anorexia, headaches, dizziness, abdominal pains, and anæmia. The attack is not accompanied by emaciation, and symptoms probably originate from mechanical irritation, not from destruction of the mucosa, though in mice, in which similar parasites cause diarrhœa, they may penetrate the submucosa. Giardia infections are intractable and may persist for years. Hegner thought that the number of these parasites is dependent upon the diet as they tend to disappear from the fæces when the patient is fed on a protein dietary.

Treatment.—It is difficult to be certain of complete extirpation of these protozoa, for giardia frequently reappear in numbers in the fæces after an absence of several months. Apparently the parasite itself is subject to periods of great activity followed by periods of quiescence.

Atebrin (*mepacrine*, *quinacrine*) is specific both for the active phases of the parasite and for the cysts. This claim, originally put forward by L. Brumpt, has been abundantly confirmed from many sources. The parasites disappear from the fæces after a course of 0·1 grm. three times daily for 5–7 days, in adults; though in children two tablets daily suffice. Sometimes it may prove necessary to repeat the course. Probably giardia is mildly pathogenic, because associated symptoms also disappear after treatment. German and Scandinavian authorities prefer *Acranil*, the hydrochlorate of an acridine compound, in doses varying from 0.25 grm. daily for children under two, to 1·5 grm. daily for 5 days in those over ten. This drug is said to be more easily tolerated than atebrin.

OTHER FORMS OF DIARRHŒA AND DYSENTERY ASSOCIATED WITH INTESTINAL PARASITES

The common intestinal flagellates, *Trichomonas intestinalis* and *Chilomastix mesnili* (*see* pp. 872–874), though occurring commonly in diarrhœic and dysenteric stools, have little claim to pathogenicity. They are frequently present in large numbers in the fluid fæces of patients convalescing from bacillary or amœbic dysenteries. Probably the presence of large numbers of these flagellates in the bowel contents is due, to a great extent, to the fluid medium, in which they flourish ; but when a case of chronic diarrhœa is encountered and no other obvious signs can be found, and where large numbers of active flagellates are lashing about in liquid fæces, it becomes difficult not to assign some pathogenic properties to these apparent agents of disease. Hence the term **Flagellate Dysentery** has arisen—a term which probably indicates that the host has been exposed to abnormal intestinal infection. These organisms usually disappear after vigorous lavage of the bowel by irrigations of 2 per cent. sodium bicarbonate combined with stovarsol (gr. 4), or spirocid, in similar dose—two tablets daily for eight to ten days.

Spirochætal dysentery is attributed to the presence of numbers of spirochætes in the intestinal canal. These organisms, composed of three or more simple spirals, are known as *Spirochæta eurygyrata*, but they are not usually regarded as pathogenic.

Intestinal coccidiosis has to be considered, especially *Isospora hominis* (*see* p. 876), which causes diarrhœa, with mucus and Charcot-Leyden crystals in the fæces. Cases of this infection have been reported from all over the world, especially from the Near East and the Dutch East Indies.

Malarial dysentery.—A blood-stained discharge or, more frequently, hæmorrhage, may occur in the abdominal forms of subtertian malaria. The blood passed is very dark, due to petechial hæmorrhages from the intestinal mucosa. These are, as a rule, very serious cases. Instances were recorded by the Editor in which malaria was first suspected from discovery of the subtertian parasite within the red blood-corpuscles in the fæces. Besides the hæmorrhagic fæces, malaria should be suggested by the clinical aspect of the patient, sweating, icteric tint of sclerotics and skin, enlarged spleen. *Violent diarrhœa* may at times be the one outstanding clinical sign of an intensive subtertian infection.

Kala-azar dysentery.—Blood and mucus may be passed in the fæces in advanced cases of this disease, which may be due to an ulceration of the bowel by Leishman-Donovan bodies. The parasites are present in large numbers in the villi of the small intestines, and may form polypoid masses in the mucous membrane of the large intestine, whence they escape into the fæces.

Other conditions which may resemble dysentery.—There are other perhaps more familiar conditions, not necessarily of tropical origin, in which dysenteric symptoms may occur.

Of all common diseases with which mild dysentery may be confused, the first place must be given to *internal hæmorrhoids*. A correct diagnosis is readily made. Again, profuse offensive diarrhœic motions with blood and mucus may be passed in *tuberculous ulceration* of the large bowel, which may be comparatively common in the tropics. *Colitis*, ulcerative, membranous, or *hæmorrhagic*, resembles bacillary and amœbic dysenteries in clinical features and in the character of the stools, but can be differentiated by microscopic examination of the fæces, as well as by sigmoidoscopy. Idiopathic ulcerative colitis (colitis gravis) is becoming increasingly common and has to be differentiated from the bacillary dysenteries. It is undoubtedly a disease *sui generis* and is distinguished by pyrexia, toxæmia, intense anæmia, a tendency to spontaneous cure, and great liability to relapse. A very acute form sometimes follows cystoscopy, or instrumental investigation of the genito-urinary tract, and has been shown to be due to mercury poisoning from instruments sterilized with mercuric cyanide. *Mucous colitis*, or the syndrome which is commonly known by that name, is a frequent *sequel* of both bacillary and amœbic dysentery and is frequently confused with both. Stercoral ulceration, produced by chronic constipation associated with myxœdema, may give rise to a blood and mucous discharge. Certain surgical conditions—simple polypus, malignant disease, intussusception, even syphilitic disease of the rectum, or rectal stricture in lymphogranuloma inguinale (p. 624), the diagnosis of which should be determined by digital examination—must be kept in mind. *Polyposis* is a very distressing condition which usually undergoes malignant degeneration. Foreign body in the rectum is another possible diagnosis.

Blood and mucus are often passed in *diverticulitis*, which is quite common in tropical practice. In *paratyphoid B.* infections ulceration of the large intestine may give rise to blood and mucus in the stools. *Food poisoning* due to organisms of the Salmonella group may sometimes cause confusion by producing the same symptoms.

CHAPTER XXIX

TROPICAL SPRUE AND HILL DIARRHŒA

Synonyms.—Tropical Diarrhœa ; Aphthæ Tropicæ ; Psilosis ; Ceylon Sore Mouth.

Definition.—A peculiar and dangerous form of chronic inflammation of the whole or part of the mucous membrane of the alimentary canal. Although a disease of warm climates, it may develop for the first time in temperate countries, usually, however, in individuals who have previously resided in the tropics or subtropics.

History.—Sprue was first described by a Dutchman, V. Ketelaer, in 1669, and then by Hillary in Barbados in 1766, but the term " sprue " was first applied to the disease when it was rediscovered independently by Van der Burg in Java, and by Patrick Manson in Amoy, China, in 1880. Since that time, it has been found to be comparatively common in the tropics. A somewhat similar steatorrhœa was described by Thaysen in 1932 in northern Europe as " non-tropical sprue."

Geographical distribution.—South China, Manila, Cochin China, Japan, Java, the Straits Settlements, Ceylon, India, Mauritius, a few cases from Fiji, more frequently in the West Indies, the Southern United States, Porto Rico, Central America, the Guianas, and Queensland. Isolated cases have been recorded from Iraq, Egypt, Gibraltar and Palestine, Malta, North Africa and Russian Turkestan. In Central Africa the disease is rare, though the Editor has recorded one instance from Nyasaland.

Epidemiology and endemiology—Information so far on this subject suggests that sprue is a regional, as opposed to a climatic disease, and it pre-eminently affects Europeans. There was formerly doubt of its existence in native races ; highly pigmented people, usually the indigenous inhabitants of the endemic country, are less liable.

The disease is apt to occur in one or more members of the same family. Many instances of sprue in husband and wife have been recorded, probably from exposure to the same influences. Atmospheric temperature *per se* has no influence, for sprue originates at high altitudes in Ceylon and in the Himalayas, where the climate approximates to that of Europe.

There are residences in Bombay and bungalows in Ceylon which are notorious for the incidence of sprue in successive tenants ; these have been known as " sprue houses " and have given rise to a popular theory that the disease is connected in some way with " dry-rot " in wooden beams.

As a rule, sprue attacks those of middle age or over. Children are rarely affected, though there is one authentic record in an English boy from Ceylon of eleven years of age (Miller). Amongst Europeans both sexes appear equally liable.

Ætiology.—In spite of the considerable work which has been devoted to this subject, and the number of speculations which have been entertained, the true ætiology of tropical sprue remains obscure. The germ causation, as for instance, the yeast, or *Monilia* theory, has now been abandoned (Kohlbrugge, 1901, the Editor 1912). These organisms are regarded more as terminal and secondary invaders. Nutritional deficiency, as originally postulated by McCarrison, Elders and Nicholls, appears at present to be the most likely factor. There are cogent reasons for including sprue in the vitamin deficiency group, or at least regarding it as essentially the result of nutritional disorder. The modern discoveries on the ætiology of pellagra and the fact that in fully-developed tropical sprue there are signs and symptoms which may be ascribed to vitamin deficiency, mainly of the vitamin B_2 complex, have fortified this theory. But tropical sprue is undoubtedly a disease *sui generis*. The clinical characteristics are so typical as to admit no other assumption.

Biochemical studies, by Fairley and others, suggest that the phenomena of tropical sprue can best be explained in terms of a metabolic breakdown of the gastro-intestinal tract, characterized by defective absorption in the small intestine, primarily connected with defective secretion of Castle's intrinsic factor by the pyloric or Brünner's glands. The well accepted fact that the anæmia of sprue resembles that of pernicious anæmia, and responds in like manner to the extrinsic factor (in liver extracts), is certainly suggestive. Then there is the glossitis, which appears to bear the same significance as in pellagra, pernicious anæmia and idiopathic steatorrhœa, in all of which it seemingly represents the expression of B_2 avitaminosis and is influenced by administration of nicotinic acid and riboflavin (*see* p. 401).

Furthermore, as in pellagra, there is a pre-sprue, or larval condition, of which glossitis is the outstanding sign, which is indistinguishable from a similar stage in larval pellagra. A connecting link between sprue and pellagra is also suggested by the fact that pellagrous symptoms may sometimes be engrafted on sprue as a secondary phenomenon as in other forms of chronic steatorrhœa.

It has been suggested, with cogent arguments, that the sprue syndrome may be regarded as the expression of "*chronic jejuno-ileal insufficiency*" of which the outstanding signs are steatorrhœa, emaciation, meteorism, glossitis and megalocytic anæmia; and that these phenomena may be evoked by a number of conditions. The main argument for this view lies in the results of gastro-jejuno-colic fistula, which reproduce the main signs and symptoms of sprue; a similar clinical picture may be produced as the result of an ill-functioning gastro-enterostomy. Sprue-like signs and symptoms disappear when the defect is remedied by operation. Sprue symptoms may also supervene on resection of four feet, or more, of the lower ileum (Markoff), or may be produced by interference with chyle absorption in lymphadenomatous infiltration of the mesenteric glands, or by ulceration of the ileum.

Other diseases closely simulate tropical sprue, such as cœliac disease in children and idiopathic steatorrhœa in adults. These are probably the outcome of other forms of malabsorption from the small intestine. In idiopathic steatorrhœa the syndrome possibly represents an exaggerated phase of tropical sprue with implication of factors other than the vitamins of the B_2 complex. It is conceivable that the syndrome is produced, not so much by the absence of essential vitamins from the dietary, as by failure to absorb them.

These vitamins are probably necessary for proper absorption of fat by the villi of the small intestine, or intimately concerned with *phosphorylation*. Stannus has attempted to explain this complicated process as follows. The absorption of neutral fat in sprue is normal, but that of fatty acid, glycerol, cholesterin and glucose is defective, due to failure of *phosphorylation*, an essential process in absorption. The fact that neutral fat and glucose are normally absorbed without the aid of this process would explain the success of strawberry and banana diet in sprue. Calcium is deficient because it forms insoluble soaps with free fatty acids, and similarly there is a deficiency of phosphorus. The loss of calcium and fats, with their fat-soluble vitamins, is responsible for bone changes, tetany and failure of blood clotting. The mass of unabsorbed fatty acid and gas, due to fermentation of unabsorbed glucose, causes distension, and is responsible for the radiographic signs of sprue and sprue-like diseases (*see* p. 541). The physiological lesion in sprue is failure of *phosphorylation* due to defect of the enzyme system, the co-enzymes of which are members of the vitamin B complex—riboflavin, nicotinic acid, pyridoxine and probably others (*see* pp. 401–407).

Tropical sprue seems therefore to be coming into line with such other well-known avitaminoses as beriberi and pellagra in which a primary and secondary form may be recognized. For instance, the sprue syndrome may reveal itself as a primary disease, or as secondary to some other infection of the gastro-intestinal tract, such as bacillary dysentery.

That there are difficulties in accepting the nutritional theory *in toto* is not to be denied ; for instance, the restriction of tropical sprue to certain tropical and subtropical countries, and the fact that Europeans who develop the disease are usually better nourished than the indigenous inhabitants of the countries where sprue occurs. Moreover, Thaysen in 1932 described " non-tropical sprue " in Northern Europe which he claimed to be clinically and biochemically indistinguishable from the tropical form. Most of his cases were undoubtedly examples of idiopathic steatorrhœa, but there remained a residuum which correspond clinically to tropical sprue and are curable by the same methods. If further research should prove this to be the case, then sprue cannot be regarded as a strictly tropical disease. In the Editor's opinion, sprue is encountered in its most florid form in the tropics and subtropics, but minor manifestations of the sprue syndrome may be encountered in temperate zones. (*See* pp. 540–541).

These views may best be illustrated by the following table :—

Syndromes characterized by Glossitis and Stomatitis.

Ætiological factors.	*Syndrome.*	*Contributory factors.*
	Ariboflavinosis.	
1. Riboflavin deficiency.	Cheilosis, seborrhœic dermatitis, glossitis, corneal vascularization, keratitis, photophobia, conjunctivitis.	

Table—(*continued*).

Ætiological factors.	*Syndrome.*	*Contributory factors.*
	Pellagra.	
1. Nicotinic acid deficiency.	Glossitis, dermatitis. Changes in spinal cord.	Bacillary dysentery, amœbiasis, intestinal tuberculosis, alcoholism.
2. Riboflavin deficiency.	Stomatitis, glossitis, seborrhœic dermatitis.	Chronic gastro-intestinal disease, sprue.
	Tropical Sprue.	
1. Adrenal dysfunction ?	Low blood pressure.	Previous gastro-intestinal disease.
2. Riboflavin deficiency.	Stomatitis, conjunctivitis, "twilight-blindness."	
3. Deficiency of Vitamin B_2 complex.	Changes in spinal cord ?	
4. Deficiency of both factors of Castle.	Megalocytic anæmia.	
	Ideopathic Steatorrhœa.	
1. Congenital defect		Cœliac disease or "consumption bowels" in childhood.
2. Nicotinic acid deficiency ?	Glossitis, stomatitis.	
3. Riboflavin deficiency ?	Glossitis, stomatitis.	
4. Other factors in the Vitamin B_2 complex ?	Megacolon.	
5. Vitamin D deficiency.	Osteoporosis, hypocalcæmia.	
6. Factors of pernicious anæmia ?	Megalocytic anæmia.	
	Pernicious Anæmia. (*Addison's*).	
1. Deficiency of intrinsic factor of Castle.	Megalocytic anæmia.	
2. Deficiency of nicotinic acid and riboflavin ?	Glossitis.	
3. Deficiency of other factors in the B_2 complex ?	Changes in spinal cord.	
	Nutritional Megalocytic Anæmia.	
1. Deficiency of extrinsic factor.	Megalocytic anæmia.	Malaria, pregnancy.
2. Deficiency of riboflavin and nicotinic acid ?	Glossitis.	

In the majority of tropical sprue cases there is either hypo- or achlorhydria, sometimes even achylia gastrica, and Castle and Townsend have shown that the intrinsic factor is absent from the gastric juice, as in pernicious anæmia ; but the gastric element differs from that of pernicious anæmia in that acidity in sprue returns to normal after adequate treatment with liver extract and restoration of the patient to health.

Pathology.—The heart has usually undergone "brown atrophy." The liver is atrophied, and all the muscles and viscera are anæmic and wasted. With these exceptions and certain changes in the alimentary tract, so far as is known, there are no special lesions invariably associated with this disease. Occasionally, the pancreas shows fatty or granular degeneration of the cells, with softening of isolated acini and slight inflammatory infiltration of the connective tissue. These, however, are not more constant than are similar changes occasionally found in the liver and kidneys. Sections of the tongue show desquamation of the epithelium, especially from the surface of the fungiform papillæ.

Lesions of the alimentary tract.—In longstanding cases, there is usually atrophy of the small bowel so as to render it almost diaphanous. Ulceration and erosion of the ileum leading to perforation and peritonitis have been described by the Editor, but these, as well as the destruction of the intestinal villi, are now thought to be secondary changes (Mackie and N. H. Fairley, and, more recently, Thaysen). The chief lesions are thinning and atrophy of the mucous membrane of the absorptive and secretory epithelium with shrinkage of the villi. The changes are essentially those of degeneration and aplasia and there are evidences of blood destruction in the mucosa, suggesting absorption of some hæmolytic substance in the intestines and destruction of blood *in situ*. In autopsies, where death has been sudden, it is surprising indeed what few naked-eye changes can be seen. Pathological changes are seen in the red marrow of the femur and the tibia. This is usually reduced in quantity, though there may be hyperplasia, as in pernicious anæmia. It is suggested that in sprue there is a toxin which primarily stimulates, but eventually exhausts the hæmopoietic system. Ulceration of the ileum, leading to perforation and general peritonitis, may be the cause of death.

The messenteric glands may be enlarged, pigmented and fibrotic. The inflammatory changes in the mucosa and the invasion by round and plasma cells, formerly considered characteristic, are now held to be inconstant in appearance and extent, and possibly to be caused by the irritability brought about by acid fæces.

Clinical pathology.—The stools of sprue are characterized by their light colour and excessive size ; they may be five or six times the normal amount. Analysis reveals the ordinary elements of bile, notwithstanding the lack of colour. The excess of fat in the stools and low fat content of the blood (412·8 mgm. per cent.) indicate that a proportion is due to actual excretion of fat through the intestinal mucosa. (The normal is 600 mgm. per cent.). Normally, neutral fats in the fæces are to fatty acids in the proportion of 1 to 2 ; in pancreatic disease this ratio is reversed, and may be as high as 15 to 1 ; while in sprue stools more splitting of fats takes place, the proportion of neutral fats to fatty acids being as 1 to 3 or even 1 to 5. It is estimated that not uncommonly 50 grm. of fat is excreted in a single stool when the patient is living on a mixed dietary. The average results of fat analysis of fæces is as follows :—

Total fat	60 per cent.
Combined fatty acids	14 ,, ,,
Free fatty acids ...	37 ,, ,,
Unsoaped fat ...	45 ,, ,,
Neutral fat	7 ,, ,,

The trypsin and other enzyme activities in the stools are normal. These figures indicate that in sprue pancreatic digestion proceeds quite normally, but that the products of digestion are not absorbed, probably because the contents are hurried through the small intestine. Malabsorption of fats may probably be due to the same cause.

The blood picture of the fully-developed sprue case is a megalocytic anæmia, the size of the cells varying from 7·8–8 μ. The very variable degrees of anæmia coincide with the variable changes in the bone-marrow. As a general rule, this grave anæmia occurs in patients over fifty years of age. In no instance, in the cases investigated, has the colour index been less than 0·7. In the majority of cases it is above that figure. In uncomplicated sprue the leucocyte counts are either normal, or there is a leucopenia associated with a relative lymphocytosis. Blood crises commonly occur in sprue and are characterized by a rapid and critical fall in the hæmoglobin and red blood-corpuscles. Usually associated with severe diarrhœa, it progresses to a fatal issue, without remissions and without those evidences of blood regeneration which are so typical of similar crises in pernicious anæmia. Hyperbilirubinæmia is found more frequently in malaria and in pernicious anæmia than in sprue. (Van den Bergh test).

The Price-Jones curve resembles that of pernicious anæmia, being characterized by marked asymmetry, broadening of the base, displacement to the right, and a definite increase of the diameter of the corpuscles to 8·07 μ. It therefore seems that deficient blood-production rather than excessive blood-loss constitutes the basis of sprue anæmia.

Serum-calcium and phosphorus content.—Fairley, Mackie and others have confirmed Scott's observations that the ionic calcium is lowered in sprue, 7·4–9 mgm. per 100 c.c. of serum being constantly registered. Fairley and Bromfield, using Kramer and Tisdall's technique, found the average total calcium was 8·8 mgm. per cent. The average serum-phosphorus reading was 3·2 mgm. per 100 c.c. so that no rise above normal occurs. It is concluded that defective absorption is the basic factor involved in the low calcium content.

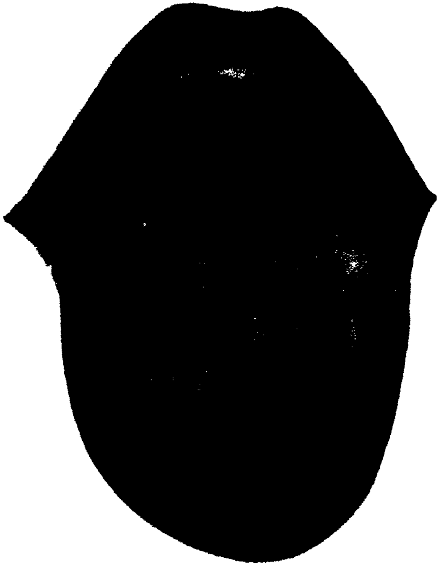
Blood cholesterol.—There is a definite hypocholesterolæmia, and Fairley has shown that the serum cholesterol averages 72·8 mgm. per 100 c.c., the lowest reading being about 40 mgm. The cholesterol content rises rapidly with liver-extract therapy and high-protein dietary.

Blood-sugar regulation.—Thaysen originally pointed out that in sprue, as well as in idiopathic steatorrhœa and cœliac disease, there is an abnormally low blood-sugar curve, which is not due to impairment of glucose absorption, or to its destruction in the intestines, but possibly is related to adrenal insufficiency.

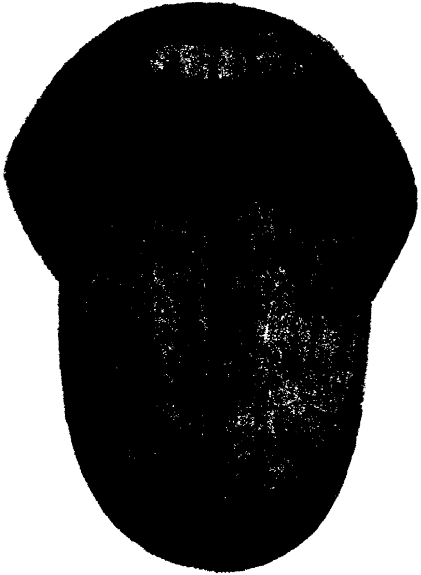
The urine is highly coloured, especially in cases with pronounced anæmia. This is due to the appearance of urobilinogen and urobilin in pathological amounts, derived from the products of blood destruction, as it is estimated that in sprue anæmia the blood-cells are being destroyed nearly five times more rapidly than normal. The diastatic reaction has been investigated and has been found to be well within the normal limits. This method affords a means by which sprue may be differentiated from chronic pancreatitis. In acute sprue there is porphyrinuria, as in pellagra.

Gastric secretion.—In most cases there is a relative hypochlorhydria or a normal acid curve, but occasionally hyperchlorhydria may be present. In cases with severe anæmia there is usually *achylia gastrica.*

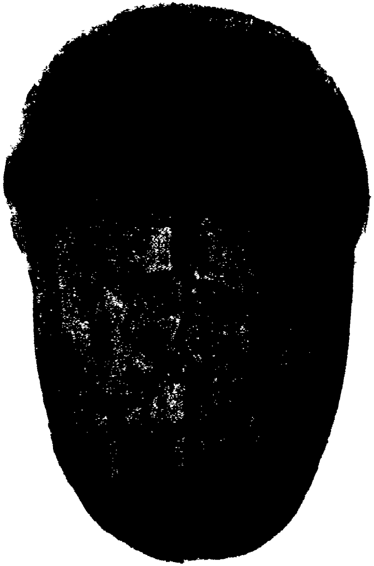
Symptoms. *Variability.*—There is infinite variety in the combination and in the severity of the various symptoms of sprue, as well as in the rate of progress of the disease. In some instances it may be almost a subacute process, running its course in a year or two; in others, again, it may drag on intermittently for ten or fifteen years. Much depends on the



Avitaminosis (B2) tongue (prepellagrous), showing angular stomatitis.



Acute stage of sprue with typical aphthæ.



Chronic sprue tongue.

(P. H. Manson-Bahr, del.)

PREPELLAGROUS AND SPRUE TONGUES.

Plate XVII

circumstances, the character, the care, the treatment, the age and the intelligence of the patient.

General symptoms in a typical case.—In an ordinary fully developed case the patient—who is generally dark or muddy in complexion and much emaciated—complains of three principal symptoms : soreness of the mouth, dyspeptic distension of the abdomen, and looseness of the bowels—the last being particularly urgent during the early morning and part of the forenoon. He may also complain of feeling physically weak, of loss of memory, and of inability to take exercise or to apply his mind. His friends will probably volunteer the information that he is irritable and unreasonable.

Mouth lesions.—The soreness depends on a variety of lesions of the mucous membrane, which, though painful, seem to be very superficial and vary considerably in intensity from day to day. During an exacerbation the tongue looks red and angry ; superficial erosions, patches of congestion, and perhaps minute vesicles appear on its surface, particularly about the edges and tip. Sometimes, from the folding consequent on swelling of the mucous membrane, its sides have the appearance of being fissured. The filiform papillæ cannot be made out, although here and there the fungiform stand out, pink and swollen (Plate XVII). If the patient be made to turn up the tip of the tongue, red patches of superficial erosion, sometimes covered with an aphthous-looking pellicle, may very likely be seen on either side of the frænum. These aphthæ probably form beneath the epithelium and subsequently burst. On eversion of the lips, similar patches and erosions are visible ; and, if the cheek be separated from the teeth, they may be seen on the buccal mucous membrane. Occasionally the palate is similarly affected ; very often, also, the mucous follicles are enlarged, shotty, and prominent. The gullet and uvula may also be congested and, in places, raw and sore.

In consequence of the irritation caused by these superficial and exceedingly sensitive lesions, the mouth tends to fill with a watery saliva, which may dribble from the corners. If the patient attempts to take any acrid food, strong wine, or anything except the very blandest diet, the pain and burning in the mouth are intolerable ; so much so that, although perhaps ravenously hungry, he shirks eating. Not infrequently, swallowing is accompanied and followed by a feeling of soreness and burning under the sternum, suggesting that the gullet, like the tongue, is also irritated, raw and tender. During exacerbations the condition of the mouth becomes greatly aggravated. Although during the temporary and occasional improvements it is much less painful, even then salt, spices, strong wines and all kinds of sapid foods sting unpleasantly ; and the tongue, particularly along its centre, is seen to be bare and polished as if brushed over with a coating of varnish. At all times the tongue is abnormally clean and devoid of fur ; during the exacerbations it is red and swollen ; but during the remissions, and when not inflamed, it is small and pointed, and, owing to the anæmic condition of the patient, it may be yellowish. The sore tongue and mouth may at first be the only signs, and they may persist for months or, it may be, for a year before complete sprue unfolds itself.

The tongue may be regarded as a mirror of the gastro-intestinal tract so that probably similar changes (hyperæmia and inflammation) are present in the stomach and small and large intestines. The mucosa of the rectum is inflamed, as the Editor has demonstrated by sigmoidoscopy.

Dyspepsia.—Dyspepsia is usually very troublesome, the feelings of weight, oppression, and gaseous distension after eating being sometimes excessive. Very likely the abdomen swells out like a drum, and unpleasant borborygmi roll through the bowel (Fig. 79). Occasionally, though not often, there may be vomiting, sometimes coming on suddenly, and not always accompanied by nausea. As a rule, there is a moderate hypochlorhydria, with adequate response to histamine, which may account for the dyspepsia. The gastroscopic appearances have been described as being similar to those of pernicious anæmia, and as taking the form of atrophic gastritis, which improves on intensive liver therapy.

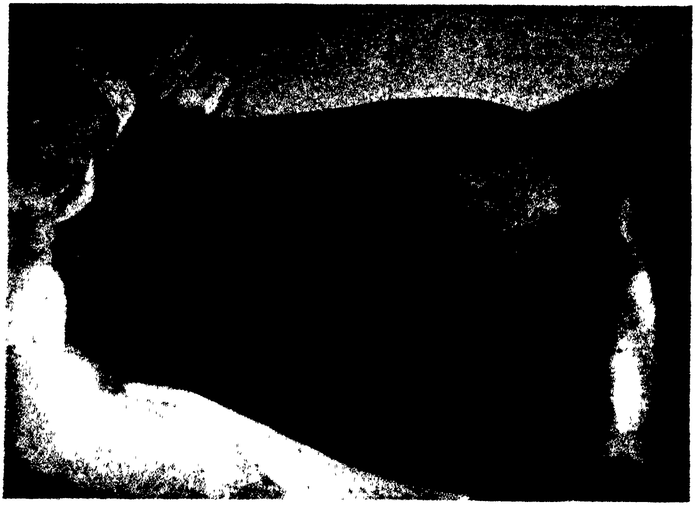


Fig. 79.—Sprue abdomen, showing intense meteorism, especially of lower quadrant.

Anæmia may be pronounced even in the early stages, though more generally it develops when diarrhœa has persisted for some time. It is a megalocytic, hyperchromic anæmia of the pernicious type, with alteration in the size and shape of the erythrocytes, very occasionally with normoblasts. Occasionally, severe anæmia, indistinguishable from that of Addisonian anæmia with high Van den Bergh readings, supervenes even when active sprue symptoms have disappeared.

Tetany associated with dilatation of the stomach is quite common in longstanding cases, but is also found in the early stages where there has been dehydration of the tissues and hypocalcæmia. It can often be elicited by compression of the upper arm (Trousseau's sign).

Cramps in hands and legs may be particularly distressing and are the accompaniments of hypocalcæmia.

Diarrhœa.—Diarrhœa associated with sprue is of two kinds: one chronic and habitual, the other more acute and, in the early stages, evanescent. The former is characterized by one or more daily discharges of a copious, pale, greyish, pasty, fermenting, acid, mawkish, evil-smelling material: the latter is watery, also pale and fermenting, the dejecta containing undigested food and, as a rule, an abnormally large amount of fat and fatty acids. In these latter circumstances diarrhœa usually brings with it considerable relief to the dyspeptic distension—at all events for a time. When the mouth is inflamed, diarrhœa is usually more active, but this is by no means invariable. The stools during periods of quiescence may be confined to one or two in the early morning or forenoon; during the later part of the day the patient is not disturbed. Even in this quiescent phase, however, they are always extraordinarily copious, the excessive bulk being attributable in great measure to fatty acids and to innumerable microscopic gas-bubbles. They are passed almost, or altogether, without pain. Not infrequently during exacerbations there may be a tender, excoriated condition of the anus, and sometimes, in women, a similar condition of the vagina, causing pruritus.

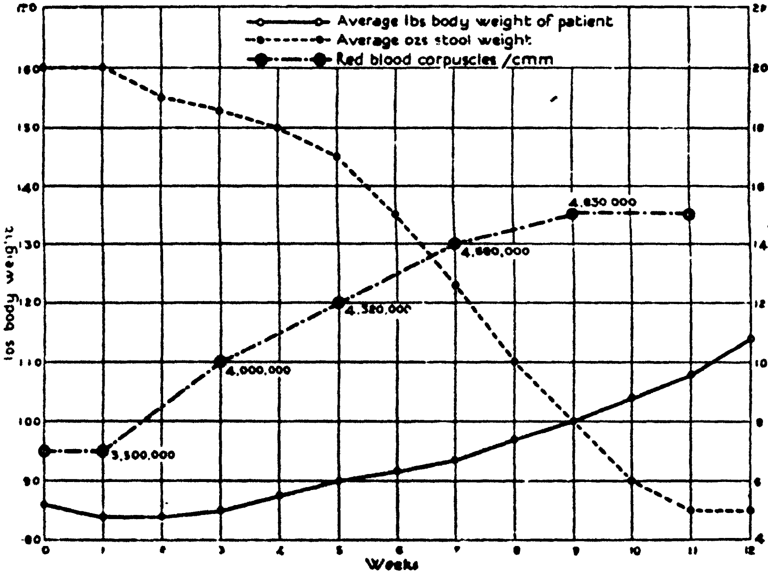


Chart 26.—Composite graph constructed from observations on ten cases, to show the relative increase in body-weight of patient and in red blood-corpuscles per cubic millimetre with coincident decrease in average weight of stool over the same period of treatment.

Types, history, course and termination. *Primary* or *protopathic sprue.*—There is a striking uniformity in the history of most cases of sprue. The patient has probably been suffering for months, or perhaps years, from irregularity of the bowels. This, the physician may be told, began, soon after arrival in the tropics, as a bilious morning diarrhœa. For a long time this morning diarrhœa went on, without interfering in any way with the general health. Later, the mouth now and again became tender, little blisters or excoriations appearing for a day or two at a time about the tip of the tongue or inside the lips. These sore spots would come and go. Perhaps, from time to time, exacerbations of the mouth symptoms would be associated with a little increase of diarrhœa. Gradually, the stools lost their bilious character and became pale and frothy; dyspeptic symptoms, particularly distension after meals, now appeared. As time went on, these symptoms would recur more frequently, and in a more pronounced form, following, almost inevitably, any little imprudence in food or exposure. The general condition now began to deteriorate; emaciation, langour, lassitude, and inability to get through the day's work satisfactorily, becoming more pronounced each summer until, finally, a condition of permanent invalidism was established.

Should the disease continue to progress, the emaciation advances slowly but surely. Diarrhœa may be almost constant, and now no longer confined to the morning hours; the complexion becomes dark, sometimes very dark; the appetite, at first in abeyance, may be ravenous, unusual indulgence in food being followed by increased discomfort, temporarily relieved by smart diarrhœa. At length the patient is confined to the house, perhaps to bed. The feet become œdematous, and the integuments hang like an ill-fitting garment, the details of the bony anatomy showing distinctly through the dry, scurfy, earthy skin. Finally, the patient dies in a semi-choleraic attack; or from inanition; or from some intercurrent disease. Such is the history of an ordinary, mismanaged case of sprue.

Another type of case commences as an acute entero-colitis or "hill diarrhœa," with sudden and profuse colicky diarrhœa, perhaps vomiting, and a certain amount of fever. The acute symptoms do not subside completely, but gradually acquire those of sprue grafted on to those of acute intestinal catarrh (*see* p. 589).

(*a*) *Gastric cases.*—Occasionally the morbid process is at first, judging from the existing clinical symptoms and subsequent history, confined to a limited part of the alimentary canal. Thus, there is sometimes sprue without diarrhœa, the principal symptoms being sore mouth, dyspeptic distension, pale, copious but solid stools, and wasting.

(*b*) *Intestinal cases.*—On the other hand, there are cases in which the mouth is not eroded and there is little or no distension or dyspepsia, but in which the stools are liquid, copious, pale, and frothy. Sometimes a patient, who may have suffered at an earlier period or on a former occasion from the first type of the disease, later acquires the diarrhœic form; and *vice versa.*

(*c*) *Sprue without diarrhœa.*—Sometimes under treatment the sore mouth, dyspepsia and diarrhœa completely subside; nevertheless, the wasting continues, the stools remaining phenomenally copious—so much so that the patient may declare that more is passed than has been eaten. In this case wasting is progressive, and the patient gradually dies of inanition.

(*d*) *Tongue or mouth sprue.*—As a rule, the characteristic appearance of the tongue is associated with gastric and intestinal symptoms, but this is not invariable. The Editor has described cases in Ceylon, and several others during the last twenty-five years, where the process remains confined to the mouth and gullet for one year or longer, before typical intestinal symptoms are noted. This stage may well be regarded as larval sprue.

Intestinal atrophy consequent on sprue.—In certain instances, under treatment the symptoms proper to sprue subside, but the patient's digestive and assimilative faculties are permanently impaired. Slight irregularities either in the quality or the amount of food, chill, fatigue, depressing emotions, and other trifling causes suffice to bring on dyspepsia accompanied by flatulence and diarrhœa. These cases may linger for years. Usually, they improve during the summer in England, getting worse during the winter and spring, or during cold damp weather. Ultimately, the patients die from general atrophy, diarrhœa, or some intercurrent disease.

Secondary sprue.—Sprue may follow closely on the heels of some other severe intestinal disease, such as amœbic or bacillary dysentery, or may be the direct sequel of hill diarrhœa. In bacillary dysentery, for instance, the sprue symptoms may be evanescent during convalescence, or, as sometimes happens, may become firmly established at some later period. Therefore, the recognition of a secondary form of sprue conforms with other nutritional diseases. The co-existence of intestinal amœbiasis with sprue has been recorded.

Sequelæ. *Anæmia and spinal symptoms.*—Severe anæmia of the pernicious type is a frequent sequel (*see* p. 534). Until recently it had been generally considered that sclerosis of the spinal cord did not occur in sprue and that this distinguished it in some degree from subacute combined degeneration of the cord in pernicious anæmia. But this distinction cannot be substantiated, for in longstanding cases of sprue with severe anæmia, occasionally unmistakable signs of cord involvement—spastic paraplegia, ankle-clonus, positive Babinski sign, and, eventually, complete and fatal paralysis of the lower extremities—have been observed. Neuritic signs in the arms and legs (pins and needles) frequently supervene ; sometimes also *neuritis*, with paræsthesia and loss of reflexes, resembling beriberi, which has been found to respond satisfactorily to vitamin B_1 therapy.

Œdema.—Generalized œdema, especially of the legs, is a frequent accompaniment of sprue, especially in those patients who are responding to treatment.

Purpuric rash.—Petechial hæmorrhagic rashes, noticeable on the thighs and legs (Fig. 61, p. 445) are undoubtedly a scorbutic phenomenon and formerly occurred in patients who had been maintained on milk. This rash disappeared after the administration of adequate amounts of vitamin C. Small subcutaneous hæmorrhages on the hands are common in atrophic cases of sprue and probably are scorbutic.

Dermatitis.—A dermatitis is a frequent accompaniment of sprue, especially in elderly people with extreme anæmia. It generally breaks out during convalescence and when the patient is responding to treatment, and is mostly seen on the arms and chest. Sometimes the rash is pellagrous, and the Editor has recorded cases of association of this disease with sprue, where improvement occurred on the administration of nicotinic acid.

Special features of sprue in women.—Amenorrhœa and menstrual disturbances are extremely frequent in women with advanced sprue. Symptoms of sprue become exacerbated during pregnancy.

Relapses of sprue are unfortunately frequent and form a characteristic feature of this mysterious disease. Often they come on suddenly, and quite unexpectedly, without any apparent exciting cause. Sometimes, in the Editor's experience, typical relapses are observed after an interval of twenty years, and in one instance twenty-seven years, of apparently normal health in England.

Latency.—One of the most remarkable features of sprue is latency. Thus, it may arise in England in persons who have at some time resided in an endemic area of the disease. Usually, this period is one or two years; sometimes it is longer—seven or eight years; exceptionally it may be as long as twenty-five years.

Diagnosis.—The tongue, the stools, and the history seem sufficiently distinctive to render diagnosis easy. Nevertheless the Editor has known cases in which the disease has been diagnosed and treated as syphilis, the condition of the mouth being attributed to this disease, and the character of the stools and other symptoms ignored. Care must be exercised in interpreting the significance of the small area of liver dullness usually found in well-marked cases of sprue. This is not due to cirrhosis of the liver, but to its wasting, in common with other organs.

Differential diagnosis.—*Cœliac disease* (Gee's cœliac diarrhœa, or the Gee-Herter syndrome) occurs frequently in Europe in children under ten, and is also seen in those of European parentage returning from the tropics. Cœliac disease is probably congenital and its ætiology is therefore different from that of sprue, but the stools are similar in appearance and in chemical composition. This disease is associated with diarrhœa and meteorism, stunted growth, and incomplete sexual development. There is no involvement of the tongue and mouth, and the anæmia is not so severe as in tropical sprue. Symptoms usually disappear on a fat-free dietary. *Idiopathic steatorrhœa* is probably the same process as cœliac disease persisting in adult life, and was regarded by Thaysen in Denmark and Northern Europe as *non-tropical sprue*. This is a nutritional disturbance associated with tetany, osteomalacia and anæmia. It is therefore characterized by disturbances of the calcium metabolism and hypochromic anæmia. According to Bennett, Hunter and Vaughan, in "non-tropical sprue" there are often various cutaneous lesions, infantilism, megacolon, fine silky hair, brittleness and ridging of the nails, clubbed fingers, and a flattened type of blood-sugar curve after ingestion of glucose (which is also found in tropical sprue). Lens opacities, gross bony deformities, and tetany constitute the outward signs of defective calcium metabolism. The serum calcium is low and there is excessive excretion of fat. Both cœliac disease and idiopathic steatorrhœa may be complicated by secondary pellagra. An important, almost diagnostic, point of differentiation, is that these two forms of steatorrhœa do not respond to liver and vitamin therapy as does tropical sprue.

The absence of skin lesions and mental symptoms differentiates sprue from *pellagra.* The sprue tongue may be difficult to differentiate from that of pellagra; the latter is pointed, and when it is inflamed and painful the process is generalized, not confined to certain definite and circumscribed areas as in sprue, and angular stomatitis is also often seen. The tongue of early pellagra (Plate XVII) is invariably associated with angular stomatitis and an atrophic condition of the lips (cheilosis). Atrophy of the lingual papillæ also occurs in pernicious anæmia and so this may be confused with sprue. No great difficulty should be experienced in differentiating *Addison's disease* from sprue. *Gastro-jejuno-colic* fistula may give rise to symptoms simulating sprue, but these disappear when appropriate surgical measures have been undertaken.

Giardiasis (*see* p. 525) may produce light-coloured fatty diarrhœa, and may be mistaken for sprue.

Differentiation of sprue from *chronic pancreatitis* may present difficulties. In the latter condition neutral fats predominate in the fæces, the tongue and mouth are not involved, and the diastatic reaction of the urine is high.

The low blood-sugar curve after the intake of 1 grm. of glucose per kilo. body weight serves to differentiate sprue from pernicious and allied *anæmias,* but a similar curve accompanies idiopathic steatorrhœa and cœliac disease. The anæmia of sprue greatly resembles that of pernicious anæmia, though normoblasts are rare and megaloblasts do not occur. High van den Bergh readings are the rule in true pernicious anæmia, exceptional in sprue. The differentiation from tropical macrocytic or nutritional anæmia cannot easily be made on blood examination alone, as the picture is very similar. This anæmia affects pregnant women in the tropics, and is not accompanied by diarrhœa.

Certain cases of *tabes mesenterica* may, on clinical grounds, resemble sprue, and so may disease of the *mesenteric glands,* such as lymphosarcoma or lymphadenoma.

The radiographic findings in sprue.—The Editor found no loss of tone in the stomach or intestines in acute incipient cases. The stomach is emptied in two hours after the barium meal, the hepatic flexure of the colon is reached in three hours, and the intestines are empty in 6–8 hours. In subacute cases there is slight loss of tone and vigour of peristalsis in the stomach. In chronic cases there is ballooning of the large intestine with some delay in the cæcum and colon. The herring-bone pattern in the jejunum described by American workers is not invariably observed as it is in idiopathic steatorrhœa.

Prognosis is good for recent cases, provided proper treatment is carried out. It is bad for patients over fifty, for longstanding cases, for careless and injudicious patients, and for those who cannot or will not take a special diet.

TREATMENT

General statement.—The treatment of sprue is mainly a matter of bodily rest and careful dieting in order to procure assimilation of the most easily absorbable foods. If treatment be undertaken sufficiently early, and be thoroughly and intelligently carried out, it is generally successful. Should, however, it be undertaken too late, when the glands and the absorbing surface of the alimentary canal have been hopelessly destroyed, the case is almost sure to end fatally. In prescribing treatment, therefore, the first thing is to get the patient thoroughly convinced of the serious nature of his complaint; for without his hearty and complete co-operation a well-established case will not be cured. To be successful, treatment must be thorough, sustained and prolonged. All predisposing causes, such as uterine or other discharges, syphilis, and helminthic infections must, of course, be removed as far as possible. The size and weight of the fæces should be estimated daily by weighing the pan and substracting from the total the known weight of the receptacle. The average daily weight of normal fæces is from six to eight ounces; in sprue it is commonly double or treble this amount. By keeping a chart of the average daily excretion, and by estimating the weight of the food ingested, an estimate may be formed of the daily intake and output.

Nursing of sprue cases is all-important. A great deal rests with the nurse; sprue patients are apt to be unreasonable and refractory, so she will need to be sympathetic and tactful, yet firm. A regular routine of feeding should be strictly adhered to, both in quantity and ingredients. The sheet anchor of treatment in sprue is diet, as all who have written on this disease agree. Fats and starches are not well assimilated.

Diet I.—The Editor is of the opinion that a combination of milk and protein meets the needs of most cases. If the tongue is very sore and the intestinal symptoms urgent, the patient is fed for the first week on a milk dietary and, if this is not easily tolerated, high protein milk—Sprulac (*see* p. 544). Sometimes, however, a mixture of milk and Sprulac may be given, or Benger's and Horlicks. When the intestinal symptoms have subsided, other ingredients may be added, as set out in the following tables:

TABLE I

First week.

Three pints of cow's milk (or Benger's Food) daily in 5-oz. feeds at two-hour intervals.

Toast, "pulled bread," rusks, with a small quantity of butter.

Total calorie value, about 1,100 calories.

TABLE II

Second week.

Three pints of milk (or Benger's Food) daily, as in Table I.

Rusks (Heudebert's or Verkade's "Groote Beschuit") and toast. Sago 6 oz.; liver soup, 12 oz. in two feeds of 6 oz. each.

One lightly boiled egg.

Weak tea or sprue tea (i.e. tea infused with milk in place of water) 8 oz.

Total calorie value, about 1,900 calories.

TABLE III

Third week and during convalescence.

Breakfast.—Porridge; 1 egg; toast (or rusks) and weak tea.

11 *a.m.*—Half a pint of warm milk, Sprulac or Benger's Food.

Lunch.—Liver soup, 12 oz.; chicken (minced), 6 oz.; spinach, 3 oz. (cauliflower, French beans, or vegetable marrow, 3½ oz.); sago or semolina pudding, 6 oz.; baked apple or banana, 6 oz.

Tea.—Toast; tea; Madeira cake, sponge cake, digestive biscuits, 3 oz.
Dinner.—Brain or sweetbread, 4 oz.; calves'-foot jelly, 3 oz.; banana, 3 oz.; arrowroot, 8 oz.
Total calorie value, about 3,900 calories.

This diet is given during the first week, with various medicinal measures; naturally it can be varied according to the needs and idiosyncrasies of each patient. The third table is instituted from the third week onwards and, during convalescence, for at least three or four months. It may be varied, of course, according to circumstances, and during the fruit season strawberries and raspberries may be added to the regimen.

In elderly patients (*i.e.*, those over 45) and where there is a high degree of anæmia, the addition of raw or underdone, finely shredded beef is of advantage.

Minced beef for Sprue Patients

8 oz. best beef;
1 good teaspoonful of marmite;
Pepper and salt;
2–3 tablespoonfuls of water.

Trim off all fat from the beef. Mince the raw beef finely, putting it twice through the mincing machine if necessary.

Place in double saucepan with marmite, seasoning, and water. Cook over boiling water, *stirring the ingredients with a fork all the time* until the meat has turned *brown and crumbly*—roughly 3 minutes.

Serve on a hot-water plate. Treated in this manner minced beef is a palatable dish.

Calorie value of 4 oz. is about 188.

In patients with flatulence and meteorism which are increased by milk, this beef diet may be substituted for one pint of milk.

Lightly-steamed meat with gravy is advantageous, and should be steamed in the following manner:

Take undercut of beef, 4 oz. Steam with 6 oz. of water for 5 to 7 minutes. Add a pinch of salt and serve as thick soup with lemon juice or slice of tomato.

The recipe for liver soup is as follows:

Take half a pound of calves' liver and cut it into small pieces. Place in a double saucepan, add ½ pint of cold water and simmer for 1½ hours. Strain through a sieve and add 1 pint of bone stock or chicken jelly, and, if necessary, flavour with marmite. Add a small quantity of pepper and salt.

Liver soup can be given in soup-platefuls of 8 oz. each, and may be taken together with underdone meat.

These methods, followed by carefully selected and increasing mixed diet, combined with warmth and rest, are the most successful ways of dealing with sprue. Food should never be given unless the patient is hungry. It is a great mistake to try to make these patients fat too rapidly, or to stimulate the desire for food by encouraging active exercise. The bowel is not in a condition to deal with large meals.

Diet 2. *High-protein dietary.*—This is especially indicated in elderly patients with inadequate assimilation, hypochlorhydria and anæmia. Alimentary rest in these cases is the therapeutic ideal and can be attained by feeding with a minimum amount of those food constituents with which the small intestine fails to deal adequately. Protein is the chief constituent, commencing with a low-calorie value and gradually increasing the quantity, while maintaining the high-protein rates. During this treatment five diets are ordered, the calorie value of which increases progressively from 770 in (*a*) to over 3,000 in (*e*), and the ratio of protein to fat and carbohydrate is maintained at 1·0 : 0·3 : 1·1.

(*a*) (Calorie value 770).
8 *a.m.*—Underdone beef, 3 oz.; juice of half an orange and glucose, 2 drachms.
12 *a.m.*—Soup, 4 oz.; underdone beef, 3 oz.; rusks, ¾ oz.; juice of half an orange and glucose, 1 drachm.
6 *p.m.*—Same as above.
(*b*) (Calorie value, 1,200).
The underdone beef is increased to 5 oz.; rusks and calves'-foot jelly added at 4 p.m. Tea, 10 oz.

(*c*).—Meals are given from 6 a.m.–7 p.m., as follows: 6 a.m., 8 a.m., 10 a.m., 12 a.m., 4 p.m., 7 p.m. The diet is much the same, with the addition of 10 oz. of tea with milk; three times daily, two baked apples and calves'-foot jelly.

(*d*) and (*e*).—The times are the same, but a greater quantity, up to 7 oz. of underdone beef is given twice daily. Bananas, custard and honey are introduced into the diet.

Protein milk diet.—As the result of biochemical investigations, it is now thought that flatulence and abdominal discomfort are in the main aggravated by fat in cow's milk. Fairley introduced a milk powder which combines the advantages of a high protein dietary with the bland properties of milk. This high-protein milk powder, or *Sprulac* (Cow & Gate Ltd.) is prepared from fresh milk which has been treated by passage through a gauze and wire filter, subsequently chilled, centrifuged to get rid of organic and inorganic débris, passed through a mechanical mixing apparatus and eventually desiccated at 120° C. The powder contains 10·6 per cent. fat; 34·0 per cent. protein and 45·0 per cent. lactose. The calorie value per ounce is 125 and the ratio of protein, fat and carbohydrate is 1·0: 0·3: 1·3. Sprulac can be given in the same manner as milk. One ounce of Sprulac is made up to 8 oz. with water and given every 2¼ hours for six feeds. Subsequently the amount may be increased and calves'-foot jelly and the juice of two oranges added. Sprulac forms an excellent addition to the diet in all stages of sprue.

Fruit diet.—The value of fruit in the treatment of sprue has long been recognized. Manson was in the habit of prescribing bananas and apples in sprue; often with marked success. Repeated trials of strawberries in sprue have to some extent confirmed their value. Bottled fruits, particularly peaches and pears, make suitable substitutes if strawberries or bananas are not obtainable. Of tinned fruits the most suitable are Libby's strawberries and blackberries, though it is doubtful whether preserved fruit possesses the same virtues as fresh. Fresh raspberries and blackberries are almost as well tolerated as strawberries. Fresh tomatoes are often beneficial. The bael fruit, or Bengal quince (*Ægle marmelos*), introduced by Fayrer in the treatment of this disease, seems to exert a beneficial effect in those countries (Ceylon and India) where it can be procured in a fresh state. During recent years it has been imported from the East on ice, and offered for sale in London. The ripe pulp can be scraped out of the hard exterior shell and eaten raw with sugar and cream, or made up with gelatin in a jelly. Two or three of these fruits may be given every day.

Return to Europe.—When sprue develops in the tropics, if feasible the patient should be sent to Europe as soon as possible. It is a mistake, however, to ship an invalid if the disease is active, or the end manifestly not far off. Diarrhœa should not be active when the patient is put on board ship. In every case provision should be made for continuation of the dietetic regimen and a supply of milk on board should be assured.

Clothing and general management.—Sprue patients returning to Europe ought to be especially careful in their clothing, and they ought to get out their warm clothes before the ship leaves the tropics. If they return during the winter, they should arrange to remain in the south of Europe until late spring. Next to an unsuitable dietary, perhaps cold is the most prejudicial influence to which a sprue case can be exposed. A sprue patient ought never to feel cold ; he ought always to wear thick flannels, thick stockings, and, when up and about, thick boots. In winter a chamois-leather sleeved waistcoat is of great service. His rooms ought to be warm. He ought to eat very sparingly. He ought never to be fatigued ; he ought to go to bed early and rise late ; in fact, he ought to do everything in his power to avoid irritating the bowel, to guard against chill, physiological depression, and copious eating.

During the summer England is suitable enough as a residence ; but during the cold winter and spring months some milder, drier and more sunny climate must be sought.

Sore tongue and mouth.—A great deal can be done to ameliorate the soreness and the dysphagia caused by ulceration of the tongue and mouth. The mouth should be kept very clean and washed out after each feed with a bland mouth-wash such as potassium chlorate, 1 drachm to the pint of hot water, but if the mouth is very painful, cocaine, 2 gr. to the ounce of glycerin and borax, brushed on to the tongue lightly before eating, will deaden sensibility. In certain cases where the saliva is very acid, as it generally is when the tongue is very raw, an alkaline mouth-wash should be used as follows :

Sod. bicarb.	gr.x (0·648 grm.)
Sod. biborate	gr.x (0·648 grm.)
Rose-water	℥iv (113·6 c.c.)

Diluted with water according to taste.

An efficient preparation for healing mouth lesions is an acriflavine dye, *Glauramine* (B.D.H.), of which the mouth-wash is made up of one teaspoonful (one drachm) to eight ounces of warm water. It temporarily stains the mouth and lips yellow. In some cases, especially where there is much sepsis, hydrogen-peroxide mouth-wash is useful. These measures should be combined with nicotinic acid and riboflavin, therapy, which undoubtedly help.

Specific treatment with vitamins.—In acute, as well as in chronic cases, the Editor has recorded success with nicotinic acid and riboflavin. Symptoms resolve in shorter time and the treatment is considerably curtailed.

Nicotinic acid is given in tablets (50 mgm.) in doses of 150–300 mgm. daily for three weeks or longer, reinforced, whenever glossitis and angular are acute, with *riboflavin*, 8 mgm. The immediate effects are in the subsidence of glossitis and rapid return of the taste-sense.

Abolition of these disagreeable phenomena exerts a profound influence on digestion and assimilation. Sometimes nicotinic acid produces a kind of histamine effect, with flushing of the face and throbbing of the arteries, but this soon passes off. This treatment also influences intestinal manifestations, but it is necessary that the diarrhœa should first be brought under control by rest in bed and suitable dietary and other measures. The most gratifying result is the abatement of flatulence and meteorism, which are usually so distressing and so persistent. It is probably wise to continue with nicotinic acid, in reservoir doses (50 mgm.), for three months or longer during convalescence.

In cases with marked hypochlorhydria the administration of hydrochloric acid is essential. A mixture containing 20 mm. of the dilute acid should be given before each main meal.

Diarrhœa.—The diarrhœa of sprue yields to dietetic treatment but, if excessive, the best method is to administer a small quantity of castor oil in teaspoonful doses, after which Batavia powder in the same quantity should be given, suspended in milk or water. If nocturnal diarrhœa is very severe, *chlorodyne* (10-15 min.) is often successful.

Batavia powder is a modification of "Peter Sys" specific (Shanghai) which was originally used by Manson and Cantlie in China. It is cuttle-fish bone combined with an iron compound. In some cases of diarrhœa during convalescence, it is advantageous to give it in wafer cachets, 15 gr., four times daily.

For less obstinate diarrhœa, Crooke's Collosol Lacto-Kaolin, in doses of one drachm daily, is recommended, while on occasions a bismuth and magnesia mixture (bism. oxycarb. 15 gr., mag. carb. pond. 15 gr. with sp. chlorof. et morph. co.) may be more suitable.

Anæmia.—No advance in the treatment of extreme cases of sprue has been so remarkable as blood-transfusion in patients in whom the anæmia resembles advanced pernicious anæmia. Some cases with a red cell count of 500,000 red cells to the c.mm. have recovered. Special precautions as regards blood groupings must be taken, and 300–400 c.c. of citrated blood injected intravenously. Sometimes two or three transfusions at weekly intervals are necessary. The modern drip-transfusion method is preferable.

The beneficial effects of liver soup in sprue have been noted since the early days of Manson and van der Burg. Since the discoveries of Minot and Murphy in 1926 it has been customary to reinforce soup by more potent liver extracts. The best are those of Eli Lilly, Parke Davis, and Oxo (Liveroid), but large quantities are required, and they are expensive. An important advance is intramuscular injection. In the Editor's hands. *Campolon* (Bayer), *Hepatex, Plexan* and *Examen* have been most efficient. In grave cases 4 c.c. is injected daily for six injections, but usually a series of 12 injections of 2 c.c. suffices. They should be made deep subcutaneously into the buttock, and are usually followed on the ninth or tenth day by a rise in the reticulocyte count. The first injections may be rather painful, but this gradually works off as more are given. Sometimes the addition of iron is of advantage, especially in cases without megalocytic blood changes. It may be given in the form of ferrous sulphate tablets (Glaxo) three times daily, or of *hæmatinic plastules* (Wyeth).

Flatulence and meteorism.—In cases with extreme distension injection of pituitary extract, especially *pitressin* (½–1 c.c.), is followed by passage of flatus and instant relief. Tablets of salol (10 gr.) and charcoal biscuits, or Charkaolin (Allen and Hanbury) in teaspoonful doses, are useful.

Constipation.—The constipation following the acute phase of sprue may be difficult to overcome. Often hard scybalæ form in the sigmoid colon and become impacted. The best aperient is castor oil. In extreme cases it may be necessary to give an enema of warm olive oil (10 oz.) and subsequently to remove the scybalæ from the rectum by the finger. As a general aperient, petrolagar (*red label*) or agarol is preferable to liquid paraffin.

Anal excoriation and irritation is sometimes a distressing feature, and may be relieved by the following ointment:

Orthoform		40 gr.
Zinc oxide		120 gr.
Starch		120 gr.
Paraffin	ad	1 oz.

Tetany and cramps.—The treatment of these symptoms, which are due to calcium deficiency, is by administration of calcium by the mouth in doses of 10 gr. three times daily, and in extreme cases by intravenous injection of salts, such as calcium gluconate (Sandoz) 10 c.c. or more.

To increase assimilation in atrophic cases.—Glucose, 2 oz. daily, should be added to the dietary throughout; and to increase assimilation when intestinal atrophy is a feature, *insulin*, 2–6 units, injected twice daily, may often be followed by an increase of the appetite and a corresponding aptitude for absorption.

Anorexia and vitamin B_1 deficiency.—The loss of appetite and taste in severe cases of sprue is a difficulty, but usually improves gradually when the patient is put to bed. It has been found that vitamin B_1 (aneurin) increases the desire for food; it may be injected, in doses of 25 mgm. daily, with advantage. It is curative also in cases presenting neuritic symptoms with loss of deep reflexes.

Hæmorrhages and scorbutic symptoms.—The Editor has treated two cases of purpuric rash resembling scurvy. This complication calls for vitamin C, either as ascorbic acid or as orange juice.

Additional methods of treatment.—Massage and passive movements are of benefit, especially in men who have been accustomed to exercise. Massage of the arms and legs should be instituted at once, but the abdomen should be left until the more urgent symptoms have subsided, when in constipated cases abdominal massage is of distinct value.

Heliotherapy and ultra-violet light radiations applied to chest and abdomen are very stimulating during convalescence in atonic and debilitated cases.

Convalescence.—Sprue patients, if possible, ought not to return to the tropics. Young adults often recover completely, but the danger of relapse is greatly enhanced in those over 50 if they return to the tropics, especially India. If compelled by circumstances to do so, they must exercise the utmost care for their health, and avoid exposure, cold baths, and all excesses; purge gently, and go on simple diet on the slightest sign of relapse. Alcohol, especially strong spirits, is strictly contra-indicated for

at least three months from the time of apparent recovery; light French wine may then be permitted.

Appended, as a guide for convalescent cases of sprue, is a diet table, which should be continued as long as possible.

Suggested Diet for Convalescent Cases of Sprue

Breakfast.
Well-boiled porridge (Quaker oats) or gruel. Sour milk (yoghourt).
Lightly boiled egg.
Toast, rusks or biscuits
Cocoa, weak tea,[1] or chocolate made with milk.
Butter in small quantities with toast or rusks.

a.m.
Warm milk or Sprulac, half a pint.

Clear liver soup, or chicken broth.
Chicken, preferably minced, boiled or roast.
Underdone minced beef.
Spinach, vegetable marrow, young peas, cauliflower, or French beans.
Milk puddings: sago, semolina.
Baked apple or banana.

Tea.
Weak tea.
Toast.
Wafers, water or Marie biscuits.
Madeira cake. Sponge fingers.

(Dinner should be the lightest meal of the day.)

Dinner (7 *p.m.*).
Brains.
Sweetbread.
Fruit or calves-foot jelly.
Arrowroot.

Fruits permitted.
Strawberries, commencing with maximum, 3 lb.
Raspberries, blackberries (as above).
Hot-house grapes.
Fruit jellies.
Bael fruit, bananas, oranges, papaya, tomatoes.
Ripe pears.

Articles of diet to be avoided.
Salmon, trout, mackerel, herrings.
Cheese.
Fresh bread.
Jams, especially marmalade.
Grease or fat.
Suet puddings.
Nuts.
Cakes with raisins.
Baked or fried potatoes.
Pastry.
Alcoholic drinks, especially spirits, gin, brandy and whisky.
Mineral waters.

Treatment of complications.—Careful search should be made for any co-existing infection from which the patient may be suffering. Malaria, especially benign tertian, and, more important still, syphilis, may prejudice recovery. Sprue patients with syphilis tolerate antisyphilitic treatment well and their general condition is benefited. Sprue may be complicated by amœbic dysentery, and in such cases vigorous treatment with emetine and emetine-bismuth-iodine may be necessary before any improvement in the general condition is noted. Acute appendicitis quite commonly complicates sprue and may necessitate operation, with the result that the underlying sprue is improved. Sometimes acute lobar pneumonia may supervene, and it has been noted that the sprue symptoms have been much improved after recovery.

Oral sepsis.—Carious teeth and pyorrhœa must be attended to after the subsidence of acute symptoms, but care should be exercised; it is a mistake to advocate too rapid extraction, as this is apt to provoke relapse.

---

[1] Sprue tea is best made with boiling milk in place of water.

HILL DIARRHŒA

Definition.—A form of morning diarrhœa accompanied by flatulent dyspepsia and the passage of copious liquid, pale, frothy stools. It occurs principally in Europeans on visiting the hills after residing for some time in the hot lowlands of tropical countries. Hill diarrhœa is a frequent precursor of the fully developed disease—sprue.

Geographical and seasonal distribution.—Crombie, who gave an excellent account of this disease in India, pointed out that a similar affection may show itself in the highlands of Europe, Africa, and possibly South America. Steen described a similar diarrhœa in Java, where it is known as "Bandoeng sprue." There is no reason, therefore, to suppose that hill diarrhœa is peculiar to India, although, owing to the large European population frequenting the hill sanatoria in that country, it has been particularly noticed there. An elevation of 6,000 feet or over, when combined with an atmosphere saturated with water vapour, is particularly favourable to its development. In India it is found to begin and end with the rains, during which, in certain years and places, it is apt to assume almost epidemic characters. Thus, during the wet season of 1880, in Simla, an epidemic of hill diarrhœa affected from 50 to 75 per cent. of the European population, three-fourths of the cases appearing within a week of each other. In some years hill diarrhœa is less prevalent than in others ; but at the proper season few of the various hill sanatoria of India are without cases.

Ætiology and pathology.—It is difficult to say what may be the precise factors determining this disease. Low barometric pressure associated with great elevation above the sea-level may be a favouring circumstance. Damp seems to be indicated by the fact that the disease occurs principally during the rains. Chill after exposure to the high temperature of the plains has possibly an important share, but hill diarrhœa is certainly something more than an intestinal catarrh. There are no adequate grounds for connecting it with either the water or the food supply, though at one time Duncan advanced the hypothesis that mica in the drinking-water caused irritation of the intestinal mucosa. There is little doubt that it is in some way connected with sprue. Steen in Java suggested suprarenal insufficiency as the primary cause, but his views have not received much support.

Symptoms.—Without very obvious cause, the patient, who in other respects may be in good health, soon after arrival at a hill sanatorium becomes subject to a daily recurring diarrhœa, the looseness coming on regularly every morning some time between 3 and 5 o'clock. The calls to stool are apt to be sudden and imperative. The motions passed are remarkably copious ; very watery in some instances, pasty in others. They are pale, frothy, and like recently stirred whitewash, so devoid are they of biliary colouring matter. Their passage is attended with little or no pain, often with a sense of relief. From one to half a dozen or more such stools may be voided before 11 a.m. After that hour—at all events, in ordinary cases—the diarrhœa is in abeyance for the rest of the day, and the patient may then go about his duties or pleasures without fear of inconvenience.

The distinctive features of this form of diarrhœa are, therefore, the regularity of its recurrence every morning and its cessation after a certain hour in the forenoon ; the absence of colour in the stools ; and the attendant flatulence. The abdomen is sometimes blown out like a drum, the patient being conscious of unpleasant borborygmi associated with a feeling as if some boiling or chemical operation were proceeding in his inside. Occasionally the stools are very pale

although there is no diarrhœa. A certain proportion of patients in whom symptoms persist develop the clinical picture of sprue.

Treatment.—The treatment recommended by Crombie, and endorsed by other medical men of experience in India, consists of a strict milk diet, rest, warm clothing, a teaspoonful of liquor hydrargyri perchloridi in water about fifteen minutes after food, and 12 gr. of pepsin, or a corresponding quantity of lactopeptin, two hours later. If, in spite of treatment, the disease persists, the patient must return to the low country.

CHAPTER XXX

INFANTILE CIRRHOSIS OF THE LIVER

A SPECIAL type of liver cirrhosis in Indian children was first described by Sen (1887). The disease appears to be peculiar to India, though a few similar cases have been reported from Mexico and North China. Cirrhosis of the liver of unknown ætiology is widespread in young adults in the tropics, especially in the East Indies (*see* p. 31).

This disease is prevalent in Hindu children. In Calcutta, from 1891 to 1893 inclusive, infantile biliary cirrhosis—the name given to the disease—caused 1,748 deaths. Although the Hindu and Mohammedan populations of that city are about equal, as many as 1,616 of the deaths occurred in Hindus, whilst only 80 occurred among Mohammedans, the balance of the mortality being among the Eurasians and other races. The disease occurs principally in children under one year, rarely attacking those over three years. Rao (1941) stated definitely that it most commonly occurs in children between the ages of six and twenty-four months, that it is not found in Moslems or Europeans, and that it occurs chiefly in vegetarian families. As a rule, it begins during dentition, or about the seventh or eighth month, running a fatal course in from three to eight months. In rare cases it may commence within a few days of birth. Instead of lasting several months, its progress may be much more rapid, and terminate in death in from two to three weeks. In India it is common in Bengal, Madras, Bombay Presidency, and the United Provinces ; it is more prevalent in rural districts than in towns.

Ætiology.—The cause of infantile cirrhosis is unknown. Neither alcohol, syphilis, nor malaria has anything to do with it. The children of the well-to-do are relatively more frequently attacked than those of the poor. It tends to run in families, child after child of the same parents succumbing within a year or two of birth. Mukerji remarked that the disease is especially apt to occur in grossly overfed and pampered children in Bengal, and has adduced evidence that the virus is probably conveyed by the mother's milk to the child. Green-Armytage believed the true ætiology to be a deficiency of vitamins in the mother's diet, thus depressing the mammary secretion and the endocrine system of the fœtus, in overfeeding of the child when born, and insufficient feeding of milch animals. Rao, who isolated *Bact. coli* from the liver and ascitic fluid, believed that the essential factors are cow's milk and the toxins of *Bact. coli*. In favour of this hypothesis, he found that the substitution of modern infant milk foods for cow's milk prevents the occurrence of further cases in cirrhosis families. One critical instance is cited of mixed twins in which the female on cow's milk developed cirrhosis, whilst the breast-fed male escaped.

Pathology.—Gibbons gave an elaborate and most careful account of the pathological anatomy of this disease ; he concluded that it is a peculiar form of biliary cirrhosis, the consequence of the action on the liver-cells of some irritant of gastric origin, which leads to degeneration of the cells in the first instance, with subsequent increase of intercellular connective tissue and, later, of the portal sheaths. The formation of new bile-ducts between the hepatic cells, which is a well-marked feature, he regarded as evidence of a natural curative effort, having for its object a regeneration of the liver-cells. Green-Armytage called the disease intercellular hepatic cirrhosis. R. Rao (1935) contributed the most profound

at least three months from the time of apparent recovery; light French wine may then be permitted.

Appended, as a guide for convalescent cases of sprue, is a diet table, which should be continued as long as possible.

Suggested Diet for Convalescent Cases of Sprue

Breakfast.
- Well-boiled porridge (Quaker oats) or gruel. Sour milk (yoghourt).
- Lightly boiled egg.
- Toast, rusks or biscuits
- Cocoa, weak tea,[1] or chocolate made with milk.
- Butter in small quantities with toast or rusks.

I *a.m.*
- Warm milk or Sprulac, half a pint.

- Clear liver soup, or chicken broth.
- Chicken, preferably minced, boiled or roast.
- Underdone minced beef.
- Spinach, vegetable marrow, young peas, cauliflower, or French beans.
- Milk puddings: sago, semolina.
- Baked apple or banana.

Tea.
- Weak tea.
- Toast.
- Wafers, water or Marie biscuits.
- Madeira cake. Sponge fingers.

(Dinner should be the lightest meal of the day.)

Dinner (7 *p.m.*).
- Brains.
- Sweetbread.
- Fruit or calves-foot jelly.
- Arrowroot.

Fruits permitted.
- Strawberries, commencing with ½lb.; maximum, 3 lb.
- Raspberries, blackberries (as above).
- Hot-house grapes.
- Fruit jellies.
- Bael fruit, bananas, oranges, papaya, tomatoes.
- Ripe pears.

Articles of diet to be avoided.
- Salmon, trout, mackerel, herrings.
- Cheese.
- Fresh bread.
- Jams, especially marmalade.
- Grease or fat.
- Suet puddings.
- Nuts.
- Cakes with raisins.
- Baked or fried potatoes.
- Pastry.
- Alcoholic drinks, especially spirits, gin, brandy and whisky.
- Mineral waters.

Treatment of complications.—Careful search should be made for any co-existing infection from which the patient may be suffering. Malaria, especially benign tertian, and, more important still, syphilis, may prejudice recovery. Sprue patients with syphilis tolerate antisyphilitic treatment well and their general condition is benefited. Sprue may be complicated by amœbic dysentery, and in such cases vigorous treatment with emetine and emetine-bismuth-iodine may be necessary before any improvement in the general condition is noted. Acute appendicitis quite commonly complicates sprue and may necessitate operation, with the result that the underlying sprue is improved. Sometimes acute lobar pneumonia may supervene, and it has been noted that the sprue symptoms have been much improved after recovery.

Oral sepsis.—Carious teeth and pyorrhœa must be attended to after the subsidence of acute symptoms, but care should be exercised; it is a mistake to advocate too rapid extraction, as this is apt to provoke relapse.

---

[1] Sprue tea is best made with boiling milk in place of water.

HILL DIARRHŒA

Definition.—A form of morning diarrhœa accompanied by flatulent dyspepsia and the passage of copious liquid, pale, frothy stools. It occurs principally in Europeans on visiting the hills after residing for some time in the hot lowlands of tropical countries. Hill diarrhœa is a frequent precursor of the fully developed disease—sprue.

Geographical and seasonal distribution.—Crombie, who gave an excellent account of this disease in India, pointed out that a similar affection may show itself in the highlands of Europe, Africa, and possibly South America. Steen described a similar diarrhœa in Java, where it is known as "Bandoeng sprue." There is no reason, therefore, to suppose that hill diarrhœa is peculiar to India, although, owing to the large European population frequenting the hill sanatoria in that country, it has been particularly noticed there. An elevation of 6,000 feet or over, when combined with an atmosphere saturated with water vapour, is particularly favourable to its development. In India it is found to begin and end with the rains, during which, in certain years and places, it is apt to assume almost epidemic characters. Thus, during the wet season of 1880, in Simla, an epidemic of hill diarrhœa affected from 50 to 75 per cent. of the European population, three-fourths of the cases appearing within a week of each other. In some years hill diarrhœa is less prevalent than in others; but at the proper season few of the various hill sanatoria of India are without cases.

Ætiology and pathology.—It is difficult to say what may be the precise factors determining this disease. Low barometric pressure associated with great elevation above the sea-level may be a favouring circumstance. Damp seems to be indicated by the fact that the disease occurs principally during the rains. Chill after exposure to the high temperature of the plains has possibly an important share, but hill diarrhœa is certainly something more than an intestinal catarrh. There are no adequate grounds for connecting it with either the water or the food supply, though at one time Duncan advanced the hypothesis that mica in the drinking-water caused irritation of the intestinal mucosa. There is little doubt that it is in some way connected with sprue. Steen in Java suggested suprarenal insufficiency as the primary cause, but his views have not received much support.

Symptoms.—Without very obvious cause, the patient, who in other respects may be in good health, soon after arrival at a hill sanatorium becomes subject to a daily recurring diarrhœa, the looseness coming on regularly every morning some time between 3 and 5 o'clock. The calls to stool are apt to be sudden and imperative. The motions passed are remarkably copious; very watery in some instances, pasty in others. They are pale, frothy, and like recently stirred whitewash, so devoid are they of biliary colouring matter. Their passage is attended with little or no pain, often with a sense of relief. From one to half a dozen or more such stools may be voided before 11 a.m. After that hour—at all events, in ordinary cases—the diarrhœa is in abeyance for the rest of the day, and the patient may then go about his duties or pleasures without fear of inconvenience.

The distinctive features of this form of diarrhœa are, therefore, the regularity of its recurrence every morning and its cessation after a certain hour in the forenoon; the absence of colour in the stools; and the attendant flatulence. The abdomen is sometimes blown out like a drum, the patient being conscious of unpleasant borborygmi associated with a feeling as if some boiling or chemical operation were proceeding in his inside. Occasionally the stools are very pale

although there is no diarrhœa. A certain proportion of patients in whom symptoms persist develop the clinical picture of sprue.

Treatment.—The treatment recommended by Crombie, and endorsed by other medical men of experience in India, consists of a strict milk diet, rest, warm clothing, a teaspoonful of liquor hydrargyri perchloridi in water about fifteen minutes after food, and 12 gr. of pepsin, or a corresponding quantity of lactopeptin, two hours later. If, in spite of treatment, the disease persists, the patient must return to the low country.

CHAPTER XXX

INFANTILE CIRRHOSIS OF THE LIVER

A SPECIAL type of liver cirrhosis in Indian children was first described by Sen (1887). The disease appears to be peculiar to India, though a few similar cases have been reported from Mexico and North China. Cirrhosis of the liver of unknown ætiology is widespread in young adults in the tropics, especially in the East Indies (*see* p. 31).

This disease is prevalent in Hindu children. In Calcutta, from 1891 to 1893 inclusive, infantile biliary cirrhosis—the name given to the disease—caused 1,748 deaths. Although the Hindu and Mohammedan populations of that city are about equal, as many as 1,616 of the deaths occurred in Hindus, whilst only 80 occurred among Mohammedans, the balance of the mortality being among the Eurasians and other races. The disease occurs principally in children under one year, rarely attacking those over three years. Rao (1941) stated definitely that it most commonly occurs in children between the ages of six and twenty-four months, that it is not found in Moslems or Europeans, and that it occurs chiefly in vegetarian families. As a rule, it begins during dentition, or about the seventh or eighth month, running a fatal course in from three to eight months. In rare cases it may commence within a few days of birth. Instead of lasting several months, its progress may be much more rapid, and terminate in death in from two to three weeks. In India it is common in Bengal, Madras, Bombay Presidency, and the United Provinces ; it is more prevalent in rural districts than in towns.

Ætiology.—The cause of infantile cirrhosis is unknown. Neither alcohol, syphilis, nor malaria has anything to do with it. The children of the well-to-do are relatively more frequently attacked than those of the poor. It tends to run in families, child after child of the same parents succumbing within a year or two of birth. Mukerji remarked that the disease is especially apt to occur in grossly overfed and pampered children in Bengal, and has adduced evidence that the virus is probably conveyed by the mother's milk to the child. Green-Armytage believed the true ætiology to be a deficiency of vitamins in the mother's diet, thus depressing the mammary secretion and the endocrine system of the fœtus, in overfeeding of the child when born, and insufficient feeding of milch animals. Rao, who isolated *Bact. coli* from the liver and ascitic fluid, believed that the essential factors are cow's milk and the toxins of *Bact. coli*. In favour of this hypothesis, he found that the substitution of modern infant milk foods for cow's milk prevents the occurrence of further cases in cirrhosis families. One critical instance is cited of mixed twins in which the female on cow's milk developed cirrhosis, whilst the breast-fed male escaped.

Pathology.—Gibbons gave an elaborate and most careful account of the pathological anatomy of this disease ; he concluded that it is a peculiar form of biliary cirrhosis, the consequence of the action on the liver-cells of some irritant of gastric origin, which leads to degeneration of the cells in the first instance, with subsequent increase of intercellular connective tissue and, later, of the portal sheaths. The formation of new bile-ducts between the hepatic cells, which is a well-marked feature, he regarded as evidence of a natural curative effort, having for its object a regeneration of the liver-cells. Green-Armytage called the disease intercellular hepatic cirrhosis. R. Rao (1935) contributed the most profound

study up to date by the application of the silver impregnation method. He concluded that the disease is a subacute *toxic* cirrhosis indistinguishable from Lænnec's cirrhosis. He emphasized the varying degrees of necrosis of the liver cells, the avascular œdematous connective-tissue network, and the obliterative lesions of the terminal and some of the bigger divisions of the hepatic venous tree without appreciable changes in the portal and biliary trees. There is also a poor attempt at regeneration of the hepatic parenchyma.

Symptoms.—Commencing insidiously, the characteristic initial enlargement of the liver may have made considerable progress before the disease is suspected. In the course of one or two months the liver has enlarged to the iliac crest. It is smooth and hard, and in some cases also the spleen is hypertrophied. Nausea, occasional vomiting, sallowness, feverishness, constipation, anorexia, irritability of temper, thirst, and languor call attention to the child's condition. Fever of a low type sets in; the sallowness deepens into profound jaundice; the stools are clay-coloured, the urine is dark with bile, and there may be a terminal ascites, with puffiness of the feet and hands. (Fig. 80.) The skin may be bronzed almost as deeply as in Addison's disease. In five months from the onset, ascites and œdema of hands, feet and eyelids appear, and in the terminal stages (8–10 months) gastro-intestinal hæmorrhages are found. Sooner or later, death from cholæmia ensues. The leucocyte count varies from 14,000 to 50,000 in the terminal stages, the increase being due to lymphocytes. The accompanying anæmia is microcytic.

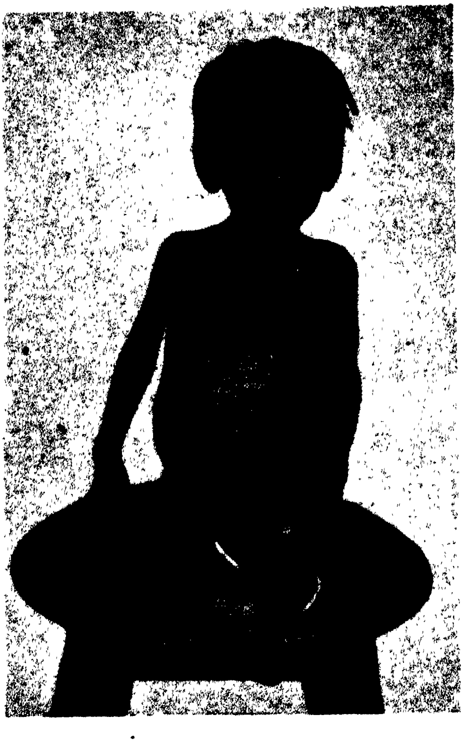


Fig. 80.—Advanced case of cirrhosis of the liver with ascites and œdema of the hands and feet, but no jaundice. (*After Rao.*)

Treatment.—According to Green-Armytage, when cases are seen early and parents are given the necessary instruction, recovery takes place in six to ten weeks. Whenever possible, in a family in which several cases of this disease have already occurred, the latest baby should be immediately removed from the mother and artificially nursed.

Prophylaxis.—The mother must be fed properly in the antenatal and nursing periods. When weaning begins, the child should be fed on specially prepared infant foods, and 2–3 oz. of fresh fruit should be given daily; iodized salt (iodosol) should be added to all food, as vegetables in Bengal are deficient in salts.

Section IV.—INFECTIVE GRANULOMATOUS DISEASES

CHAPTER XXXI

LEPROSY

Definition.—A chronic infective granulomatous disease produced by the leprosy bacillus, characterized by lesions of skin, nerves and viscera, ending in local anæsthesia, ulceration and trophic lesions. After a prolonged course it is usually fatal.

History.—The ancient history of leprosy is wrapped in the mists of time. It has been thought by some that the Egyptian records of 1350 B.C., in the reign of Rameses II, refer to this disease, although Rüffer found no evidence of leprotic mutilation in thousands of mummies he examined. In the same way, the writings of Confucius in China may possibly refer to leprosy, but is it certain that the Biblical accounts really concern the disease as we know it to-day ? When leprosy reached Greece it was first known as elephantiasis, but Aristotle in 345 B.C. clearly described its malign signs and symptoms. History relates that it was unknown in Italy until the return of Pompey's legions from the East in 62 B.C. Galen wrote of the disease in Germany in A.D. 180. Spain became contaminated by Roman troops in the fifth and sixth centuries, and by the ninth and tenth it was common in France. Thereafter, there is some mention of the disease in England, leading to the establishment of the first leper hospital in Nottingham in A.D. 625. In due course it appeared in Wales, Scotland, the Shetlands, Faroe, Iceland and Greenland but, probably, while it was most prevalent in Western Europe in the Middle Ages, it began to decline during the fourteenth and fifteenth centuries. It was endemic in Ireland up to 1775, and the last British leper died in Shetland in 1798. At present it still simmers in the Iberian Peninsula, Norway, the Baltic Provinces, Southern Russia and Turkey. With the discovery of the West Indies and the American Continent, leprosy spread to the Western Hemisphere, where it was previously unknown, and for this the nefarious influence of the slave trade must be held primarily responsible.

This sorry tale, however, pales in contrast with the rapidity of its extension in the Pacific during the latter part of the nineteenth century. Introduced by Chinese into Hawaii in 1848, it spread like wildfire. The most serious outbreak was in New Caledonia, where it was introduced in 1863, and two years later one-quarter of the population had been attacked.

Epidemiology.—Various estimates have been made of the total number of lepers in the world. From official figures, admittedly incomplete, they number about 2,500,000, but this is undoubtedly an underestimate, and the true figure is probably about four to five millions. The most striking fact brought out by Rogers and Muir, in their study of climatic factors, is that every country with a high rate of incidence (5 per mille and over) is in the tropics and possesses high annual rainfall and a considerable degree of humidity. The state of civilization and culture amongst these coloured peoples is low, and they live in small overcrowded houses under conditions of semi-civilization favourable to the spread of this disease.

The highest incidence is found in tropical Africa. The estimated rates per mille of population are 20 in Belgian Congo ; 16 in French Equatorial

Africa, and 5–10 in the British West and Central African colonies. In tropical Asia and Oceania a high rate of prevalence occurs, with rates varying from 2–22 per mille (New Caledonia and the Marquesas). In the Western Hemisphere the incidence varies from 1 in the West Indies to 3·75 in Colombia, Venezuela and Brazil. The world-wide relation between rainfall and leprosy incidence is seen in the noteworthy fact that leprosy is almost completely absent from those parts of the tropics with a rainfall of less than 10 inches per annum.

In temperate climates and in North Europe the rate appears to be nowhere over 1 per mille with the exception of parts of India, China and the Southern portion of Japan, in areas with a comparatively high rainfall. The explanation of these basic facts appears to be that dry heat is inimical to the survival of the lepra bacillus outside the human body. According to Rogers and Muir, the evidence of accumulated data favours the view that the organism generally invades the body through the skin.

Rogers has furthermore suggested that mild tuberculization of a community producing an exalted immunity to the tubercle bacillus also affords some protection to leprotic invasion, *although the reverse is certainly not the case*, as it is common knowledge that lepers often succumb to pulmonary tuberculosis.

Predisposing factors.—The most important factors influencing the prevalence of leprosy are a low stage of civilization and accompanying grave hygienic defects. This was shown by the disappearance of leprosy from amongst a number of infected Norwegian immigrants into the United States when leprosy died out as a result of the greatly improved hygienic conditions under which they lived. It has become clear, moreover, that there is little or no tendency in leprosy to spread at the present day under favourable hygienic conditions in temperate climates. Defective housing and overcrowding furnish favourable conditions for its spread, and in the main endemic areas the poorer inhabitants live in close proximity to one another. One fact that has been brought out strongly in the Hawaii reports is the effect of irregular sexual relationship with native women, and in the Marquesas Islands epidemic leprosy was spread by the prevailing promiscuity. Sociability, too, has been found to favour its spread ; thus, in Norway Hansen recorded that formerly it was considered impolite to refuse to sleep in the same bed as a leper, if he was not in an advanced and noticeable stage of the disease. The habit so prevalent in the Pacific Islands of smoking communal pipes and of eating out of the same dish naturally also favours infection. Absence of fear of the disease, as in native tribes of Central Africa and in the Pacific, and their objection to isolation of lepers naturally encourage direct contagion.

Diet is said to predispose to leprotic infection, especially the edible yam root—colocasia—in the Pacific Islands.

Epidemic diseases, such as typhus or plague, attended by a high general mortality, have in the past resulted in great, though temporary, decrease in prevalence of leprosy.

Ætiology.—The universal and ancient conviction of the infectious nature of leprosy is accepted everywhere, but during the nineteenth century there existed a deep-rooted belief in the almost exclusive origin of leprosy through heredity. Native belief for centuries in China, Japan and Central Africa has been moulded on the heredity theory, but it was held that this taint does not make its appearance until puberty.

In St. Kitts Munro found, in 64 cases with reliable family records, that there was no family history in 34, whilst of the remainder there existed a direct history in 9 only. During the past decades much positive evidence has been obtained against the heredity theory. First, there is the diminished fecundity of lepers, which is well known. The rapid increase of leprosy in Hawaii could by no means be explained on any hereditary basis. The most striking example, however, in history is the observations of Hansen on 170 Norwegians who migrated to Minnesota, U.S.A. when suffering from the disease; not one of their descendants, up to the third generation, had contracted leprosy in America.

Contagion.—It is generally accepted that leprosy is conveyed from the sick to the healthy by contagion, and this is emphasized by all who have written on this subject, such as Brousse in Trinidad (1879), Hills in British Guiana (1881), and Leloir in the Hawaii reports of 1886. A native of a non-leper colony may acquire the disease on visiting a leper country and, moreover, may communicate it to his fellow countrymen on his return. One well-authenticated instance occurred in 1872 when an Irishman, who became a leper in the West Indies, returned and conveyed it to his brother in Dublin. The Editor studied a somewhat similar case in a woman whose husband—a Mauritian—had died of leprosy, and who developed the disease in London, where she had lived all her life, after an incubation period of seven years.

Intimate contact appears to be necessary, combined with lowered resistance and susceptibility to infection, because implantation of the bacillus does not alone suffice. Many attempts have been made in the past to communicate leprosy to man by inoculation; all, with two questionable exceptions, have failed. De Langen (1936), however, reported the case of a European in Java who was injected with morphia from a syringe previously used on a leper; six months later a leprous nodule appeared on the forearm at the exact site of the morphia injection; subsequently, lepromatous manifestations were noted. In June, 1936, Lagoudaky was twice inoculated intramuscularly with leper blood. Some forty-four days later two small subcutaneous leprous lesions appeared and he was demonstrated in 1938 at the International Leprosy Congress.

The rapid spread of leprosy in a susceptible community is difficult to reconcile with the statement that in many instances contact under favourable circumstances has failed to convey the disease. Thus, in those who have lived for a long time in attendance on lepers there have been only a very few instances of infection, e.g. the historic cases of Father Damien at Molokai, and two Sisters of Mercy and the Medical Superintendent at Robben Island in South Africa. But hundreds of attendants on lepers pursue their work for years unscathed. In Louisiana 19 Sisters of Charity have been in attendance on lepers for 41 years without one single instance of infection.

As with tuberculosis, evidence points to the susceptibility in early life.

The relationships involving intimate contact in childhood are most important. This has been realized in the Culion Island leper colony (Philippines) where children of lepers removed from their leprous surroundings do not contract leprosy. Amongst 10,000 lepers there Denny noted that 35 per cent. were brothers and sisters, 27 per cent. cousins, 11 per cent. children of lepers, 7 per cent. parents of lepers but only 1 per cent. husband and wife. In Japan it is recorded that 7 per cent. of children of lepers contract the disease.

Bacillus lepræ (*Mycobacterium lepræ*).—This organism is the accepted cause of leprosy and is present usually in great profusion in the tissues. In size, shape and staining reactions it closely resembles the tubercle bacillus. It exhibits marked pleomorphism; the ends are somewhat attenuated and by some it is said to possess a gelatinous capsule. Individual bacilli vary in size, from 1·5 to 5 μ in length and from 0·2 to 0·5 μ in breadth. Curved forms with pointed ends are not uncommon. In the reactionary stages of the disease the organisms may be granular, coccoid, mono- or bipolar. Round, spore-like bodies often impart a granular appearance to a clump of bacilli. In common with the tubercle and smegma bacilli *Myco. lepræ* is acid-fast, retaining carbol fuchsin stain after being treated with mineral acids, though it may be distinguished from *Myco. tuberculosis* by being more easily decolorized by alcohol than by weak acids. Moreover, it occurs in large numbers in the lesions, chiefly in zooglœa masses within the lepra cells, often grouped together like bundles

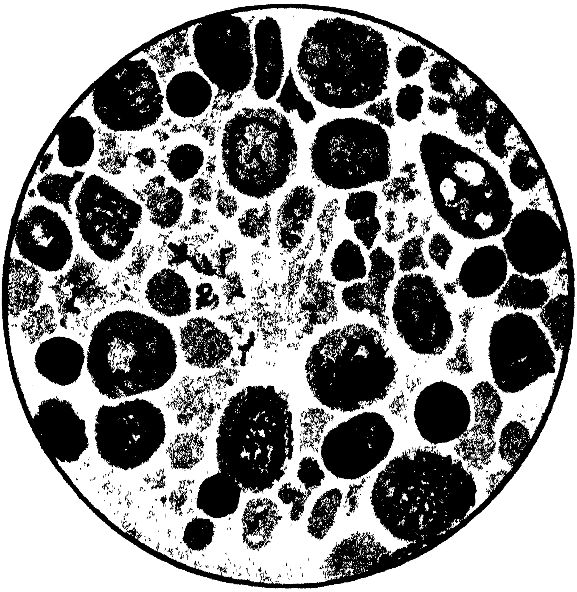


Fig. 81.—Section of spleen showing lepra cells and lepra bacilli. × 800.

of cigars or arranged in a palisade. Chains are never seen. Most striking are the intracellular and extracellular masses, known as *globi*, which consist of clumps of bacilli in capsular material. (Fig. 81.)

The bacilli can be readily demonstrated by excision of a leproma, or they can be obtained by clamping a nodule, pricking the solid tumour, collecting a droplet of expressed " leper juice " on a coverslip and staining by the Ziehl-Neelsen method. They are Gram-positive. They are found in all primary deposits, in the skin lepromata, in marginal infiltration of the macular eruptions (where they may be very sparse), in apparently normal skin in the vicinity of leprous lesions, in the early stages of leprous neuritis (where also they may be present in small numbers) and in the specific lesions in the liver, spleen, testes and lymphatic glands. In the blood vessels they have been found in the endothelium and occasionally free in the blood, or engulfed by leucocytes. This fact is specially useful in diagnosis when thick dehæmoglobinized blood-films are stained by Zeehl-Neelsen stain. Bacilli are also abundant in the purulent and mucoid discharges from the nose, as well as from ulcerating lepromata. Very rarely have they been found in the spinal cord or lungs.

Cultivation of *Myco. lepræ*, though repeatedly attempted, has never been really successful. Some investigators, it is true, have obtained growths of acid-fast bacilli (chromogenic and non-chromogenic), or diphtheroids, which in some instances have developed acid-fast forms on subculture. Others have described branching bacilli, granular and coccoid forms.

It is probable that all four varieties (diphtheroid, pigmented acid-fast, apigmented acid-fast and acid-fast streptothrices) have been more or less commonly encountered in leprous tissue in various parts of the world. When some of these cultures are injected transient granulomatous lesions have been obtained, but there is general agreement that they do not constitute true leprotic lesions.

Inoculation of animals with human leprous material containing prodigious numbers of organisms does not give rise to typical progressive leprous lesions. Adler (1937) succeeded, to a limited extent, in communicating leprosy to young splenectomized Syrian hamsters (*Cricetus auratus*). A fragment of lepra nodule was inserted under the skin and, when the animal was later killed, leprosy bacilli were demonstrated in the liver, and (in other animals) in neighbouring enlarged and caseating glands, but he failed entirely to carry on the disease by subinoculation in a continuous series of hamsters. Similar results have been obtained by Burnet. Subsequently Dharmendra and Lowe in India, in a series of carefully planned experiments on the same animals, by implantation into the abdominal wall and intraperitoneal inoculation, failed to produce generalized or progressive infection. When the nodule was implanted into the abdominal wall, masses of bacilli were found at the site of the implant, but not beyond, and bacilli were found elsewhere in two animals only. The fact seems to be that lepra bacilli can survive for long periods in inoculated animals and even dead bacilli may evoke local reactions and produce pathological appearances similar to those produced by living organisms. Araujo in Brazil appears to have had experiences similar to those of Adler and to have found the organisms in the European hamster (*Cricetus cricetus*) in great profusion. Collier (1940) implanted lepromatous material beneath the skin of monkeys fed on a diet of *Colocasia* (Yam) over a long period. It is claimed that some developed symptoms reminiscent of leprosy in man and that acid-fast bacilli were obtained from material procured from the ears of these animals.

Rat leprosy.—A leprotic disease of the rat, which occurs naturally throughout the world, was first observed by Stéfansky in Odessa in 1903. Two types are recognized: disease of skin and muscle and disease of lymphatic glands. In tropical rats it occurs commonly and has been specially studied by Lampe and de Moor in Java. House rats are usually affected, especially *R. rattus concolor* and *R. decumanus*. Infection in these animals is conveyed by injury and by cannibalism. Laidlaw succeeded in transmitting this disease to the Syrian hamster, and it can also be conveyed to rats of the same species, infection taking place readily through skin abrasions and subcutaneous inoculation. The bacillus is *Mycobacterium lepræ murium*, morphologically indistinguishable from *Myco. lepræ*, whilst the lesions resemble those of human leprosy, macroscopically as well as histologically. Attempts at cultivation have shown much the same negative results as in human *Myco. lepræ*.

In spite of the general similarity of human and rat leprosy, it is generally agreed that the organisms represent two separate and distinct species and there does not seem to be any connection between this disease of the rat and human leprosy.

Pathology.—*Spread of leprosy through the body.*—*Myco. lepræ* enters the skin either by direct inoculation, or by spread from another focus, possibly carried by wandering cells. Passing through the capillary walls, the bacilli lie in the perivascular lymphatics or are ingested by endothelial cells and histiocytes. The process is difficult to follow in the case of macules with scanty bacilli, which spread centrifugally. The bacilli pass from the cutis to the main nerve trunks by the lymphatic channels and are found lying singly or in groups between the nerve fibres. Metastatic spread through the bloodstream and auto-inoculation through abrasions also occur. Bacilli have been found in the corium of the skin over almost the whole body. It was formerly supposed that they were absent from the soles of the feet and palms of the hands, but this is incorrect; macroscopically, the lesions are inconspicuous in these situations owing to cornification of the skin.

In advanced lepers the mucous membrane of the nose, mouth and pharynx are affected, and the eye frequently, both superficially and deep. The lungs, even in the most advanced stages, escape to a great extent. The liver is usually invaded, and bacilli are found in the interlobular connective tissue and around the central veins. The interstitial Kupffer cells are swollen with bacilli, which, however, do not penetrate the parenchyma cells.

In acute advanced cases the spleen is often involved, especially in the arterial sheaths and the Malpighian bodies. The glands at the hilum are frequently infiltrated. Small numbers of bacilli have been demonstrated in the œsophagus, stomach and intestine, with involvement of corresponding lymph glands. Absence of intestinal ulceration characterizes leprosy. In nodular leprosy the bacilli may be present in the glomerulus of the kidney, when they may cause hyaline degeneration and interstitial nephritis, which is quite common in leprosy.

In a large proportion of cases of nodular leprosy of prolonged duration albuminoid or lardaceous disease of the alimentary canal, liver, spleen and kidneys ensues.

The suprarenals are attacked in all cases in which the liver and spleen are affected. The testicles are to a great extent destroyed in all nodular cases by inter- and intra-tubular invasion. The testicular tissue is finally completely destroyed.

Leprous affection of lymphatic glands is histologically obvious. The glands are swollen, but without alteration of form. On section, the ampullæ and medullary cords are yellow, or yellowish-brown, which renders them unmistakable. The inguinal glands are especially affected and the lower members of the group may be as large as pigeon's eggs. Microscopically, the ampullæ and trabeculæ are filled with *globi*: evidently lymph cells which have become filled with bacilli. The circulation through the glands is not arrested; nevertheless, they retain their infectious products. Suppurating lymph glands are, not infrequently found in skin leprosy, especially in the groin and neck. On the other hand, especially in the Pacific Islands, these glands may be tuberculous, or may even contain both leprosy and tubercle bacilli.

Distribution of bacilli in skin and nerves.—In the skin the leprosy bacilli may be destroyed by the tissues of the body; they may be latent, or they may multiply and spread. The vessels of the corium are arranged in two plexuses: the superficial or subpapillary and the deep or subcutaneous. These communicate through vessels adjacent to the hair-follicles and sweat glands. The subpapillary plexus supplies branches to the papillæ; the deep communicates with arterial and venous vessels lying in the subcutaneous tissues. Nerve-plexuses correspond to those of the vascular system.

The spread of leprous infection in the corium takes place in the lymphatic channels. In some lesions the superficial plexus and its papillary branches are involved, in others the whole thickness of the corium. In others again spread is primarily along the deep plexus, invasion of the superficial layers taking place along the hair follicles, resulting in the pebbly appearance of some tuberculoid leprosies.

The central nervous system is seldom the site of leprous lesions. When secondary degeneration of the spinal tracts takes place it is due to extreme destruction of peripheral nerves, but the spinal and Gasserian ganglia have been found to contain bacilli. Septic abscesses of the larger nerve trunks, especially the ulnar, are sometimes found.

Wherever leprotic infection advances there is a general or local reaction on the part of the tissues to arrest the invasion. In the lepromatous type this reaction is generally limited, but in the neural it may be pronounced, and the leprotic process may remain for years confined to a single lesion.

Lepromatous (nodular) leprosy.—Young lepromata present a smooth, white, glistening appearance on section, but the older appear browner. The specific lesions of leprosy differ from that of tuberculosis, inasmuch as they are well supplied with blood vessels and never undergo caseation. The earliest recognizable lesions are generally multiple, the result of bacillary metastasis from some unknown reservoir. The more acute the process, the more numerous the foci. Lesions are classifiable as nodules, papules, macules and diffuse infiltration.

Nodules, round elevations of skin of limited size, may be temporary or permanent, soft vascular or fibrous. The nodule is probably formed at the site of a bacillary embolus, either in normal skin or in a portion already infiltrated with leproma. (Figs. 82, 83.)

Papules are smaller than nodules, not larger than a split pea.

Fig. 82.—Egyptian child, aged 11, showing acute early nodular leprosy. (*Dr. H. K. Giffen.*)

Macules are roughly circular or elliptical patches of discoloured skin, and are found in both the main types of the disease.

Diffuse infiltration of the skin is often noted without the appearance of nodules or macules. It is due to infection of the skin at numerous points accompanied by cellular infiltration, but response to the invading bacilli is insufficient to produce clinically noticeable signs. In resolving lesions the skin may assume a thin atrophic appearance resembling crushed parchment.

The essential cell in defence against leprosy is the macrophage (histiocyte).

There seems to be an allergic element in tissue response in leprosy. The early reaction to *lepromin* is probably allergic, but it is not clear that the late, true reaction is the same. The lepromin test is usually negative in lepromatous cases, positive in tuberculoid and nervous cases, and usually positive in child contacts, especially in the later years of childhood.

When the resistance of the individual is high, characteristic histological changes are : concentration of round cells, especially round hair follicles and vessels and development of the "tuberculoid focus," similar to tuberculosis. The essentials in the histology of the skin in resistant or neural leprosy are : localization of the process in the skin, the foci being chiefly perifollicular and perivascular ; formation of epithelioid and giant cells ; invasion of the subcutaneous nerves.

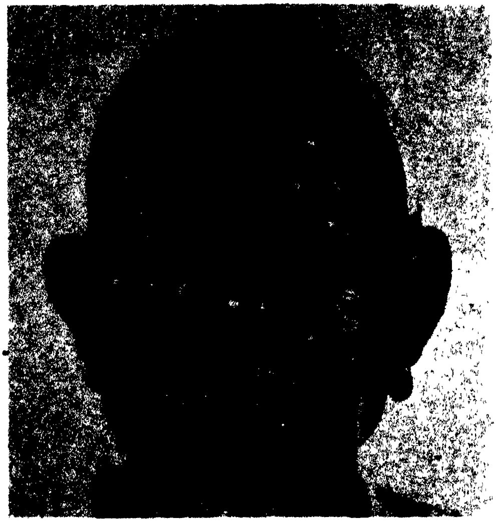


Fig. 83.—Nodular leprosy in an Egyptian.
(*Photo, Dr. H. K. Giffen.*)

The histopathology of the nerve lesion corresponds to that of the skin. In advanced lepromata bacilli and lepra cells are more abundant and there is formation of fine fibrous tissue in the endoneurium which may later contract and block the nerve-fibres. In the neural type bacilli are few, though it is easier to find them in nerves than in the skin. The cellular reaction also tends to be more intense so that epithelioid and giant cells are present in greater or lesser numbers surrounded by small round cells. Thickened nerve trunks may become enclosed in a dense fibrous sheath which may later cause constriction.

In the non-resistant case the essential cell is the macrophage but, as the bacilli multiply, so no attempt is made to localize infection, owing to the relatively lowered resistance of the tissues. The bacilli multiply rapidly, the macrophages become active and phagocytose the bacilli. These are the "lepra cells" which are uniformly distributed beneath the epidermis (see Fig. 81, p. 556).

In lepromatous leprosy there is no centralization of " lepra cells " in the granuloma ; nerves in the cutis stand out and do not appear to be invaded. As this process continues, the invasion of the cutis becomes more intense, and all the skin elements become involved and eventually unrecognizable, so that the epidermis becomes flattened, and the whole subcutaneous tissue, including the subcutaneous fat, is invaded by the granuloma. The lepra cells now appear to give up the attempt at phagocytosing the bacilli and undergo a curious foamy degeneration (foamy cell of Virchow). There is marked absence of gross invasion by lymphocytes. Owing to the ease with which the bacilli multiply they are carried by the lymphatics throughout the body and there is general dissemination and multiplication, especially in the reticulo-endothelial system (Fig. 84.)

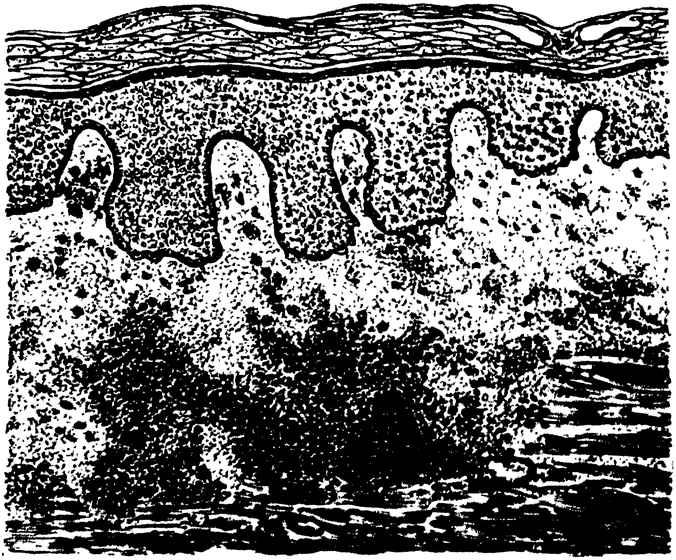


Fig. 84.—Early lepromatous lesion, showing diffuse infiltration of sub-papillary, and dense infiltration of sub-epidermal layers.

Tuberculoid lesions.—The epithelioid cell is distinctive of the tuberculoid lesion, not only in the skin, but also in the nerves ; it seldom, if ever, contains lepra bacilli. Indeed, it is usually difficult, or quite impossible, to find bacilli in this type of lesion. The so-called " giant cell of Langhan's " is another characteristic, and occasionally a few bacilli are found in connection with it. This cell may be of considerable size and is found in skin and nerve tissue surrounded by numbers of small lymphocytes. In typical tuberculoids the cellular elements are arranged in dense cords, which in section resemble tubercles (Fig. 85).

The activity of lesions is indicated by abundance of typical epithelioid cells, and in major tuberculoid the inflammatory process may be so acute that necrosis and ulceration of the skin take place.

Immunity.—Contrary to the popular belief, there seems little doubt that there is a natural immunity to infection which varies in degree in different individuals. Susceptibility to infection may depend upon general health, because it is certain that debility from any cause lowers resistance to leprosy. Varying individual resistance is also exemplified by the type of the disease. The nerve type, with tuberculoid lesions and few bacilli, indicates a comparatively high resistance and the multibacillary lepromatous form a comparatively low resistance. In the former, Mitsuda's skin (lepromin) test is usually strongly positive, in the latter negative.

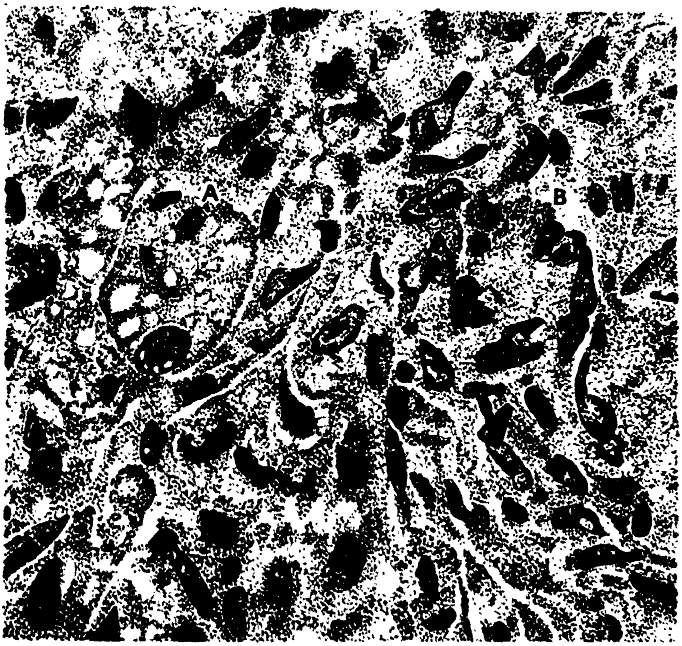


Fig. 85.—Early lepromatous lesion, showing large foamy cell (A) in the deeper tissues and a leprotic giant cell (B). The main cells are epithelioid in type. (*After Cochrane.*)

The suggestion has been made that this test may be employed in non-leprous subjects as an index to resistance to leprosy. Applying it to non-leprous children of leper parents, Rotberg found that positives increased with increasing age, reaching the maximum of 50 per cent. at the age of ten. This is taken to indicate that resistance is low in young children, but increases with age, but there is no evidence, as in tuberculosis, that resistance may be ultimately broken down by massive or repeated infections, whilst slight infective doses tend to raise resistance. Another indication of resistance is the abortive case, when slight, though definite, lesions appear and disappear without apparent cause. About the inheritance of acquired immunity there is still little clear knowledge.

In Burma leprosy is of a much more severe type in native Burmese than in Indians living in that country. Some authorities have claimed that racial immunity is the result of prolonged and intimate contact with leprosy at some remote period of history and its disappearance as an endemic disease has been explained on this basis, but there is really little evidence to support this. It is more natural to explain the persistence of endemic leprosy in certain European countries, and its disappearance from others, on the basis of improved sanitation and hygiene than on racial immunity.

Localized immunity is observed in active lesions, especially those of the tuberculoid type. In the annular form of eruption the active inflammation spreads at the margins while the disease dies down at the centre, leaving only a slight discoloration or perhaps a mild sensory impairment; or, again, a major tuberculoid lesion may flare up and die down again, leaving only a slight visible scar to indicate its former site.

Probably the majority of humans are non-susceptible to leprosy save during the critical years of childhood and adolescence. Even when infection does take place there is a natural tendency to recover, so that the possibility of arrest in the initial stages has only been realized in recent years. Cochrane has shown that in children more than 50 per cent. of all neural lesions show improvement over a period of three years; possibly this is related to the lepromin reaction, as the great majority give a positive result.

Clinical features.—*Primary infection.*—The early manifestations of leprosy may be vague and indefinite, such as malaise, weariness and mental depression. The probability is that bacilli reach the corium of the skin, or mucosa of the nose, mouth or pharynx, through some breach of the epithelium. It is difficult to be certain whether the primary lesion is the initial one, or some metastatic manifestation but, when several appear on widely-separated parts of the body at the same time, they naturally represent secondary lesions derived from some primary focus. Rogers stressed the following points as worthy of notice. In hilly and stony districts in India the primary lesions are most commonly observed on the feet. No lesions of the scalp are recorded. The first lesions on the body are scattered most densely on the extensor surfaces, especially on those parts exposed to pressure when lying down, such as the cheeks, outer surfaces of the shoulders, arms, buttocks and outer surfaces of the thigh. The flexor surfaces, on the other hand, are remarkably exempt. The affected parts are just those most exposed to insect bites and to the excoriation by the nails in attempt to allay irritation.

The fact that leprosy is more prevalent in hot, moist climates may to some extent be explained by the greater softness and moisture of the skin and the frequency of prickly heat. In cold climates, when the body is protected by clothes, it appears that a larger proportion are inoculated through the nasal mucosa. The face around the nose is a frequent site of *leprides* which are devoid of lepra bacilli; the nasal mucosa is frequently involved and is probably the immediate site from which the leprides arise.

Incubation period.—This is undoubtedly very variable and may be very prolonged: as long as 6 to 8 years. In South Africa the average period in nodular cases is about 2 years though it would be fair to state that the general average is 8½ years, the extremes lying between 5½ months and 4 years. It may well be that very long incubation periods may represent long latent periods after infection and before outward visible signs become apparent. Early discoloured anæsthetic patches may be overlooked for years.

In children of lepers living with their parents in the Culion Island colony in the Philippines it was observed that the disease developed in 22 children within 4 months to 4 years from the time of their removal from the source of infection. Certainly in one case it took place during the first year of life. Muir has recorded a case in a three months' old child. There appears to be direct relationship between closeness of contact with the diseased and the early development of symptoms. The length of incubation is considerably affected by the general health and habits of the patient, as well as by the climate. The first signs of leprosy may appear during the course of some other disease, such as dysentery, enteric fever, malaria or influenza.

As compared with tuberculosis, one of the chief characteristics of leprosy is the absence of toxicity; enormous numbers of bacilli may be present in the body with few signs. The local inflammatory reactions to lepra bacilli vary within wide limits. Thus, in one patient the disease is so localized that it affects one small skin area or the main nerve supply. There may be acute inflammatory swelling, local pain, trophic, sensory and other disturbances. Bacilli can be demonstrated with great difficulty. In contrast, a second case may show involvement almost of the whole body, so that a preparation taken from any part of the skin may reveal numerous bacilli though the patient is not acutely ill, and is able to be about and do his work. The nerves are not noticeably thickened, and superficially the skin appears normal. At any stage during invasion sudden exanthematous reactions may appear, accompanied by fever and general symptoms.

The *chronic onset* is so gradual and insidious that the disease has advanced to a considerable extent before any abnormality is evident. There may be tenderness, tingling or thickening of a nerve, an area of anæsthesia, perhaps with some change in the appearance of the skin, insensitiveness to burning, formication, tingling or numbness of extremities. Discoloured skin patches may be mistaken for eczema or ringworm; these may at first be small, gradually increasing in size.

In the *acute onset* there are occasionally multiple lesions with less diffused margins, which tend to spread rapidly and which contain very numerous bacilli. The first noticeable sign may be an evanescent rash. The onset may be determined by some other acute disease, such as malaria or typhoid, which lowers the resistance. It may also be the sequel to chronic infection, such as syphilis, ancylostomiasis or chronic disease of the gastro-intestinal tract. The period of life may also have some bearing, *e.g.* extra strain imposed on the body during puberty, parturition and menopause.

The clinical types of leprosy.—Though leprosy affects the whole system, its lesions are more manifest and conspicuous (1) in connection with skin and mucous membranes and (2) in the peripheral nerves. In the more acute forms, with low resistance and prodigious multiplication of bacilli, the clinical signs are mainly connected with the formation of the "leproma"—a granulation with lepra cells. In textbooks of general medicine this form is referred as to "*nodular*" leprosy. The second main type is known as *neural* and is chiefly characterized by polyneuritis and macules. It is usually more chronic and benign and is associated with greater resistance. In this form *Myco. lepræ* is difficult or impossible to demonstrate in the skin lesions. According to the recommendations of the International Leprosy Congress in Cairo (1938) the following subdivisions are recognized:—

1. *Lepromatous* 1 (*L.*1).—(Nodular).—Slight lepromata consisting of one or a few macular areas or a few small infiltrated patches, small nodules, or diffuse lepromatous changes; no lesions of nasal mucosa.

2. *Lepromatous* 2 (*L.*2).—Moderately advanced cases with numerous macular areas or fairly numerous small or larger infiltrations or nodules. Lesions of nasal mucosa frequently present.

3. *Lepromatous* 3 (*L.*3).—Advanced lepromatous (nodular). Cases with numerous, extensive, or very marked lepromatous lesions, which vary in their stage of development or retrogression. Lesions of nasal mucosa invariably present.

4. *Neural* 1 (*N.*1).—
   - (*a*) Cases with from one to several small macules, or a smaller number of larger ones (flat or elevated), without indications of polyneuritic changes.
   - (*b*) Cases presenting only polyneuritic changes of slight degree with minor trophic disturbance.
   - (*c*) Cases showing combinations of macular and polyneuritic manifestations.

5. *Neural* 2 (*N.*2).—
   - (*a*) Cases with fairly numerous or large macules without evidence of polyneuritic changes.
   - (*b*) Cases presenting only polyneuritic changes of moderate degree and peripheral anæsthesia of considerable extent.
   - (*c*) Cases showing combinations of equivalent total degree.

6. *Neural* 3 (*N.*3).—
   - (*a*) Cases with numerous and extensive macular lesions with polyneuritic changes.
   - (*b*) Cases with polyneuritic changes, such as extensive peripheral anæsthesia, marked motor and trophic disturbances, ulcers and mutilations.
   - (*c*) Cases showing combinations of equivalent total degree.

Whilst this classification aims at describing the two main types, it is common to find both present at the same time. The case is then known as "mixed." The degree of advancement of each type is indicated by symbols, for instance, L_3—N_2. L_1—N_3.

Relative frequency of the types.—In India and Africa and also apparently elsewhere, the neural type preponderates, forming 55 to 90 per cent. of the total.

Polyneuritic lesions.—Involvement of peripheral nerve trunks produces sensory changes in the extremities, which commence distally and spread in a proximal direction. They result in trophic changes, such as anidrosis, glossy skin, keratosis, perforating ulcers, atrophy, necrosis of bones and mutilations of the extremities.

Lesions of peripheral nerves.—Thickening of nerve trunks is related to mechanical injuries. The ulnar nerve is commonly affected at the elbow, while the radial is well protected. Thickening of the branches is generally correlated with leprides of the neural type.

Leprous nerve abscess is not uncommon in India associated with the neural type, or with injury. It occurs in superficial nerves—usually the ulnar, median cutaneous of forearm, great auricular or crural. The abscess is usually central and spindle-shaped and contains pus similar to that of glandular tuberculosis. Lepra bacilli may be present.

Leprides is the term applied to macules of the neural type and polyneuritic lesions caused by involvement of large nerves. They assume the form of minor tuberculoid or major tuberculoid macules and are characteristic.

Anidrosis, preceded by hyperidrosis, may be one of the first noticeable signs.

Hypopigmentation, usually noticed in highly pigmented skins, is not usually complete, as in leucoderma, but partial.

Hyperæsthesia, with an area of the lesion tender to touch and painful stimuli, precedes anæsthesia.

Anæsthesia. At first it consists of loss of epicritic and then of protopathic sensibility.

Parakeratosis is recognized clinically by changes in the horny layer of the skin which becomes shiny and scaly.

Hyperkeratosis is best seen on the palms of the hands, or soles of the feet, and in the latter situation perforating ulcers usually form.

Hair and nails.—The hair follicles are affected ; the hairs become soft and thick, breaking off at their point of emergence. The broken end becomes club-shaped, but growth continues inside. Similar changes take place in the nails, which become thickened and curved and claw-shaped.

Vascular changes produce congestion and erythema, usually surrounding the margins of the lesion.

Resistance is the determining factor whether the type becomes neural or lepromatous ; the latter invariably shows greater concentration of bacilli in both nerves and skin. The lepromatous lesions are in the main symmetrical. Leprides and anæsthetic patches of the neural type are less so. When they cover large areas it is the result of gradually extending lesions from comparatively small foci.

The "lepra" reaction is acute in onset and course, accompanied by severe, febrile constitutional symptoms when all the lesions suddenly become swollen and inflamed. At the same time fresh nodules or macules, surrounded by œdema, appear, and cutaneous or subcutaneous nodules become pustular, break down and discharge pus full of *Myco. lepræ*, many of which are diphtheroid in shape and staining reactons. As the reaction subsides, the lesions remain covered with desquamating epithelium. This reaction may last a few days, or may be prolonged for weeks or months.

It may remain confined to the face or extend to the whole of the body. The factors which determine its onset are not so easily ascertained.

Intercurrent disease, such as malaria, may light up the lepra reaction and, moreover, in the lepromatous form, small doses of potassium iodide may produce a similar condition, but these symptoms usually rapidly fade with elimination of the drug from the body. In India there seems to be a predisposition to the lepra reaction, which is much less common in Central Africa. In the neural type the reaction differs, as the tuberculoid form of lesion is more limited so the febrile and toxic symptoms are less severe.

In both the main forms of leprosy the reaction represents an attempt to destroy the causative bacilli. In the minor tuberculoid form this is often successful when bacilli are scanty, but in the major tuberculoid, where they are more numerous, it is not. In the lepromatous form the reaction is less severe when there are masses of bacilli to be destroyed and so, as the result of toxic absorption, the patient's resistance is reduced and the lesions become even more widespread than before.

The process spreads to the nerve-trunks and ramifications. The nerves become swollen, congested and tender, and there are neuralgic pains. Blisters and bullæ may be formed, with ultimate sloughing, which may even proceed to bone necrosis. Perforating ulcers in the feet are frequently the result of nerve reaction in the lower limbs. Herpes zoster may accompany involvement of the intercostal nerves.

Distribution of leprous lesions.—Those parts of the body most exposed appear to suffer early. In Europeans these are the hands and face. In natives exposed to injury the feet are most liable.

Head and neck.—The ears are more constantly affected than any other part, and in a suspected case it is always as well to look first at the auricles, where any thickening of the lobule may be readily detected by palpation with finger and thumb. Nodular lesions are seldom seen on the palms of the hands or soles of the feet and are exceptional on the penis and scrotum. The scalp was formerly said to be seldom affected ; this is partly due to its anatomical structure, and partly to the fact that it is hidden by hair but, as a matter of fact, leprous alopecia is by no means uncommon. In the neck the cutaneous branches of the nerves are early involved, especially the great auricular, which may stand out on the skin and be quite conspicuous. Palpation of this nerve may be a great help in early diagnosis.

Initial lesions of all types are common on the face, especially on the forehead. There is often loss of hair of the eyebrows, especially the outer part, and of eyelashes, even in the early stage of the disease. Lesions of the nasal mucosa are often present, though they may pass unnoticed unless specially sought. They may cause nasal catarrh and often intermittent epistaxis. There may be merely a diffuse erythema, or erythematous patches, or general infiltration leading to corrugation of the skin. Nodular eruptions appear on the eyebrows, leading to leontiasis, and there is often a characteristic thickening of the nose. In the neural form anæsthetic patches appear, together with paresis or paralysis of groups of muscles, which create a peculiar mask-like expression (Fig. 86). When the orbicularis palpebrarum is affected the results are serious, as failure to close the eyes involves trauma of the cornea. Paresis of the sphincter muscles of the mouth leads to dribbling. The senses of taste and smell may either be much diminished or lost entirely. Pressure on the facial nerve frequently causes intractable facial paralysis.

Lesions of the eyeball may be divided into two categories: those due to the presence of *Myco. lepræ* in the eye, or those due to interference with the nerve supply.

When *Myco. lepræ* are present in the eye, lesions are caused by spread either along the lymphatics or bloodstream. It is not uncommon for the disease to spread from the face to the conjunctiva, which becomes injected and thickened. When diffuse, this process may at first resemble ordinary conjunctivitis. Later, nodules appear, which may be mistaken for pterygium. The disease may attack the cornea, which is the most vulnerable tissue; then a ground-glass pannus spreads inwards over the pupil from the corneal margin and may considerably interfere with vision. Leprotic nodules of the cornea are by no means uncommon and, when deeper, may bulge into the anterior chamber. Again, leprotic infiltration may spread from the sclera along the anterior ciliary vessels, setting up iridocyclitis resembling that of syphilis. When there are nodules of the iris the eye

Fig. 86.—Leprotic infiltration causing paresis of facial muscles and paralysis of orbicularis palpebrarum.

is doomed. The eye may also be affected by blood-borne infection, when isolated nodules may appear on the cornea or in the vitreous, but it is rare for the retina or optic nerve to be affected when other portions of the eye remain exempt. In Rogers's experience in India, from 5–10 per cent. of lepromatous cases develop disease of the eye or its adnexa.

In the neural type the eye is often involved in an area of widespread tuberculoid or lepride. Healing is followed by sclerosing fibrous tissue. Anæsthesia of the cornea and the deposition of fibrous laminæ, together with paralysis of the palpebral muscles, abolish the corneal reflex and prevent normal closing of the eye by day or night, so that progressive ulceration of the cornea takes place, and general panophthalmitis may occur. Ectropion leads to eversion of the punctum lachrymale and discharge of tears, with eventual destruction of the lachrymal sac.

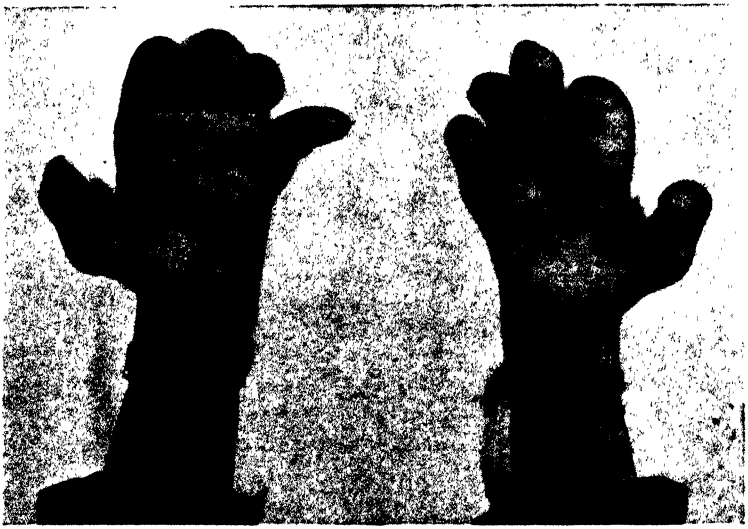


Fig. 87.—Nerve leprosy : main-en-griffe. (*Dr. H. K. Giffen.*)

The nose.—The habit of "picking" the nose, especially in children, probably plays a part in lesions of the mucosa, and those parts of the nasal septum and inferior turbinates within reach of the fingers are most commonly affected. All degrees and types of infection which occur in the skin are found in the nasal mucosa ; nodules may be present on the turbinates, ulcers and scars on the septum. Perforation of the septum and deformity of the nose may result. When there is ulceration, the discharge contains large numbers of *Myco. lepræ*, so that these cases constitute a serious source of infection to others.

Mouth, pharynx and air passages.—Lesions of the lips are sometimes found as an extension from the face. Nodules appear at the outer margins of the lips, and fibrous constriction may cause partial stenosis. Nodules of the tongue are seen in advanced cases. The palate may be affected by diffuse or nodular lesions. Perforation of the palate may occur in the absence of syphilis. The larynx is not primarily affected, but may be involved by extension ; the onset is usually insidious. In some lepromatous leprosy the soft palate, uvula and ary-epiglottic folds are swollen and indurated ; tubercles of various sizes may appear. Later there is ulceration ; constriction of the glottis may necessitate tracheotomy. Fibrous constriction is the cause of the hard whispering voice of the confirmed leper, giving rise to the brassy leprous cough. In primary nerve leprosy the throat is seldom affected. Lesions of the pharynx and tongue are exaggerated during the reactionary phase.

Upper extremities.—Primary lesions are not uncommon; in those who wear European dress they tend to be limited to the hands. The flexor surfaces tend to be much less affected than the extensor, possibly because they are more liable to injury.

Skin and nails.—The nails are not usually affected in the early stages. In the lepromatous type the most marked changes occur when there is deep infiltration of the skin of the fingers. The nail becomes attenuated and there is longitudinal ridging of the nail-bed. In the nutritional lesions of the neural type the nail is thickened and tends to split transversely. Trophic blebs and blisters on the hands are frequently the result of burns and bruises to which the anæsthesia exposes them.

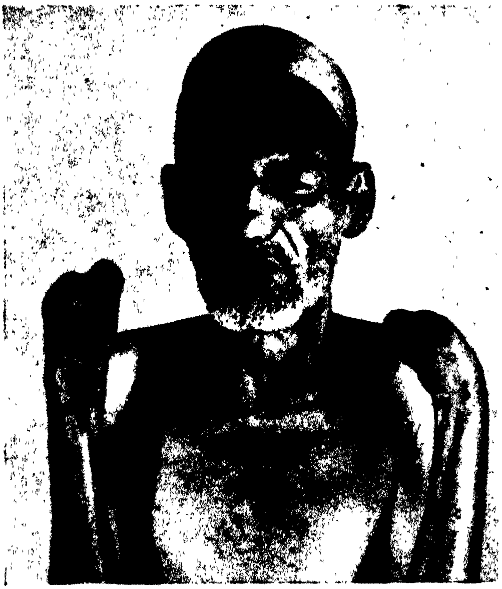


Fig. 88. Late effects of nerve-leprosy of 22 years' duration. *(Dr. H. K. Giffen)*

Muscles.—Muscular atrophies are most conspicuous in the neural type, chiefly from involvement of the ulnar nerve. Thus, the intrinsic muscles of the hands are affected, with flattening of the thenar and hypothenar eminences so characteristic of ulnar palsy. The characteristic *main-en-griffe* is a later development, with hyperextension of the metacarpo-phalangeal and flexion of the interphalangeal joints. The whole deformed hand becomes rigid, as if carved out of wood. Finally, with overgrowth of the nails and progressive osteoporotic changes in the phalanges, it becomes the typical leprous claw hand, like some deformed vulture's talon. Wrist drop may develop, chiefly from disuse ; as the bones shorten, a claw-like nail may often be implanted into a metacarpal. There is seldom any affection of the upper arm (Fig. 87).

Bones.—Decalcification and osteoporosis of the bones accompany the neural form. The phalanges become atrophied, and may actually become absorbed without sepsis or open wound. The metacarpals are less often affected. The process is often complicated by sepsis, and consequently necrosis of bone (Fig. 88).

Lymph glands.—In skin leprosy there may be enlargement of the axillary or inguinal glands. This may be due either to invasion of *Myco. lepræ* or septic organisms.

Lower extremities.—Initial lesions in natives commonly occur on the feet, and a patient may suffer from the more chronic types without noticing much amiss. Often the first sign noted is a bleb or blister. The superficial peroneal nerve, as it passes round the head of the fibula, is specially affected and is felt as a thickened and palpable cord. Drop-foot resulting from peroneal paralysis is not uncommon. The posterior tibial nerve is also frequently involved. The pretibial skin is stretched, shiny and hairless ; it does not sweat but usually becomes excessively dry and cracked. In others, again, there is elephantoid swelling of the feet extending to the knees, with depigmented anæsthetic patches, horny hyperkeratosis and mutilation of the toes.

Perforating ulcers of the soles of the feet are painful and crippling ; they are associated chiefly with neural cases and are the direct result of nerve involvement. The epithelium of the sole becomes thickened and inelastic. This leads to fissuring of the skin and the formation of ulcers. The feet become flattened and painful, owing to destruction of the musculature of the arch, and the anæsthesia may permit many injuries. Trophic changes in the muscles and periosteum lead to decalcification and absorption of the bone, which may be even more extensive in the foot than in the hand. Thus, the astragalus is often completely absorbed. Sepsis through cracks and abrasions is a terminal event. Nodules on the legs are most frequently found at the sites of injury or friction. They are especially common on the internal and external malleoli. Lymphangitis in the lower limbs is not uncommon.

Body and internal organs.—Lesions on the trunk do not differ in any essentials from those on the extremities. The middle line is less affected as a rule. Lesions on the front of the chest are said to be comparatively rare. In nerve leprosy typical herpetic lesions containing *Myco. lepræ* have been reported. Induration and even hypertrophy of the nipples are very common in the reactive stage, followed by retraction in the phase of resolution. It is said in India that, when the lower abdomen is protected by a loin cloth, lesions of the abdomen are confined to the upper half (Fig. 89).

Lesions of lungs have not been recorded. Large quantities of purulent sputum are due to bursting and discharge from nodules in the trachea and upper bronchi. Pulmonary tuberculosis not infrequently complicates the more severe forms of leprosy. Lepra bacilli are commonly found in spleen and liver, but do not seem to give rise to any special symptoms.

Genital organs.—Testicles are affected in advanced cases. Sterility is more common in males than in females, and it is rare for the ovaries to be involved. Swelling of the male breast (*gynæcomastia*) commonly occurs in cases in which the testes have been destroyed. The birth-rate amongst lepers appears to depend on the fertility of the male.

Lymphatic glands are enlarged in the vicinity of gross infections of a part, especially in the neck, axillæ and groin.

Resolution.—Leprous lesions may resolve spontaneously. Major tuberculoids may disappear, with deposition of scar tissue. Minor tuberculoids often heal up at the centre, with little change in the texture of the skin. In the lepromatous type, nodules which resolve leave flat scars like deep burns.

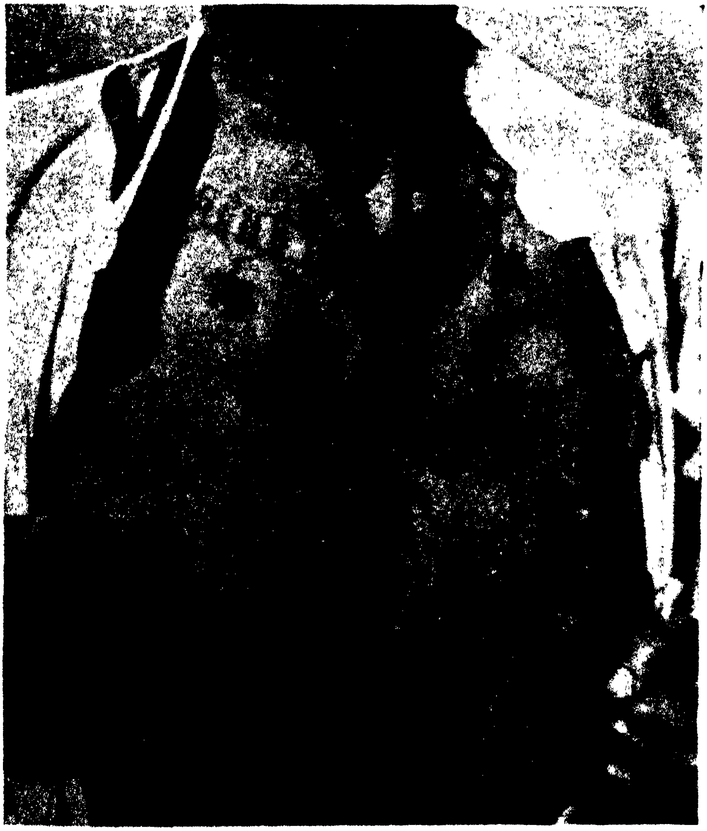


Fig. 89.—Leprosy, showing hypertrophied nipples.

Incidence.—Leprosy is more common in men and assumes a more severe form. In Norway the few remaining cases are chiefly in females, which is explained by their greater longevity and the milder character of their disease. Before the age of puberty children of both sexes are almost equally affected. The periods of puberty and childbirth impose a severe strain and increase somewhat the incidence in the female. The chief factor in the considerable excess of male cases is the greater freedom they enjoy. As in tuberculosis, the majority of cases are infected during the first two decades, and probably few contract the disease after 40.

Little is known about the factors of race, susceptibility and resistance. Differences which have been observed are probably explicable on climatic, social, dietetic and economic grounds. In India and Africa leprosy is especially common and severe in races with mixed European blood. That the social condition has a marked influence on the incidence and severity of leprosy is self-evident. In Norway it was formerly confined to fisher-folk living under very primitive conditions, but in India wealthy and highly-placed people are quite commonly infected. Rogers is of the opinion that in these it is a result of bed-infection.

Duration.—When leprosy is acute and febrile it may be fatal within two or three years, but in the great majority the course of the disease is very slow.

Diagnosis.—Early diagnosis is of the utmost importance, but many factors militate against it. It is, of course, easy to diagnose obvious and advanced cases. The ignorance of the patient, his dread of the disease, and the fear and superstitions of the general public may hinder prompt recognition. The earlier indications are the discoloured patches on the skin, and symptoms referable to involvement of the peripheral nerves, such as tingling or numbness, formication, or a feeling of woodenness in the limbs. In the majority of cases the first lesions noted are depigmented anæsthetic patches. Of fundamental importance are impairment of sensation, thickening and tenderness of nerves and demonstration of acid-fast bacilli.

To test sensation, the patient should be stripped and blindfolded. For testing anæsthesia to light touch, a feather should be used ; analgesia is tested by pin-prick ,using an area of normal skin as control. Loss of thermal anæsthesia is important. Hyperæsthesia and paræsthesia may precede anæsthesia to light touch.

Thickened nerves may be felt on palpation, and tenderness elicited by striking an area sharply with the finger or patellar hammer. The ulnar nerve is commonly affected above the elbow, the superficial peroneal at the head of the fibula behind the knee ; the radial as it curves round the humerus, or its branches as they pass over the lower end of the radius ; the posterior tibial below the inner malleolus ; the great auricular as it runs parallel to the external jugular vein and the branches of any particular nerve supplying a tuberculoid lesion. Examination of a smear for *Myco. lepræ*, by cutting down on the epineurium of a nerve, may occasionally be necessary.

Bacteriological examination.—In tuberculoid macules bacilli are difficult to find, and should be sought at the margins. In the lepromatous form, where there are no outstanding nodules, the lobule of the ear is the site of choice. Lymphatic gland puncture, as well as the examination of blister fluid by carbon dioxide snow, may be useful.

Biopsy of the skin may be made by smears made from a " snip " or by section. The scraped incision method of Wade consists of pinching-up the skin and applying compression to stop bleeding. With a small scalpel a cut 5 mm. long is made well into the infiltrated layer. All blood should be wiped away and, with the blade transverse to the incision line, the side and bottom of the cut should be scraped repeatedly, and the material spread on a slide and examined. The selection of the site is important, though *failure to find bacilli in one smear does not justify a negative diagnosis.*

Examination of the nasal mucosa is as important as that of the skin, and frequently a positive result is obtained when the skin is negative. A sharp-pointed tenotomy knife is the best instrument, and material should be sought in the septum and inferior turbinate. If there is ulceration, slight scraping suffices. Otherwise, a small piece of mucous membrane should be scraped off. Cotton swabs should not be used, as they frequently harbour saprophytic acid-fast organisms which may be mistaken for *Myco. lepræ.* The standard Ziehl-Neelsen method should be used for staining.

Rubino's reaction.—The blood sedimentation is constantly increased in leprosy and, concurrently, the cholesterol content of the blood is reduced (Westergren's method with citrated blood). Rubino has advocated an agglutination-sedimentation test with formolized sheep's corpuscles. The serum is said to contain a specific substance which causes rapid agglutination and sedimentation of these corpuscles. It is claimed that the reaction is specific and sedimentation is produced in less than one hour.

The lepromin reaction (Mitsuda).—In early lepromatous cases this reaction is usually positive, and resembles clinically and histologically the Mantoux reaction in tuberculosis, but it may not become apparent for several days (p. 577). It is an allergic response. Ota and Nitto have recently advocated, as giving better results, an antigen prepared from granulomatous deposits in the heart muscles of hens injected with human leprosy material. Cochrane found the lepromin reaction positive in 60 per cent. of neural and 100 per cent. of tuberculoid cases. Lepromatous cases are usually negative. Some healthy children give false positive reactions.

Subsidiary signs.—Anidrosis, often preceded by hyperidrosis, is characteristic of chronic cases, and is usually present in tuberculoid macules. In doubtful cases pilocarpine, 1 in 1,000 solution, is injected intradermally in a suspected patch and a similar amount in adjacent healthy skin. Both areas are then painted with tincture of iodine and, when dry, powdered with starch. The control area sweats, turning the starch blue. Absence of sweat at the point of injection indicates leprosy.

The histamine test of Rodrigues is somewhat similar in slight or early cases. A drop of 1 in 1,000 solution of histamine is placed within the margin of the suspected area, and a second outside. A prick is made with a needle through the drop. A red flare appears in normal skin.

Parakeratosis, hyperkeratosis, ichthyosis and alopecia.—These first three conditions are interconnected and are due to malnutrition followed by changes in the stratum corneum. The surface of the skin is shiny with scales. Hyperkeratosis is best seen on the palms of the hands and soles of the feet where the epithelium becomes abnormally thick and is apt to split, forming a superficial perforating ulcer. Somewhat similar changes take place in the nails, whilst loss of hair in the beard, eyebrow area and scalp are well known.

Differential diagnosis.—The characteristic marks of leprosy are sufficiently distinctive, but they have to be differentiated from psoriasis, seborrhœal dermatitis, various forms of tinea, eczema, lichen ruber planus, pellagra and filarial disease. Blastomycosis produces skin lesions reminiscent of leprosy. From syphilis and yaws, however, it may not always be so easy. Syphilitic and yaws skin lesions may often closely resemble the maculæ of leprosy, but the absence of sensory changes and reaction to treatment are sufficiently distinctive. The Wassermann reaction alone cannot always be depended upon in differential diagnosis. Syphilis and leprosy frequently co-exist. In mild early cases of leprosy positive reactions denote coincident spirochætal infection, but in advanced cutaneous and neural cases, especially those subject to lepra fever, a positive reaction does not necessarily always indicate a syphilitic infection. Lloyd, Muir and Mitra reported that 68 per cent. of nodular and 27 per cent. of neural cases in adults gave positive reactions.

The thickened skin of crab yaws on the feet may roughly resemble leprotic hyperkeratosis and may give a semblance of anæsthesia. Gangosa of yaws may be mistaken for nasal leprosy.

The early lesions of *mycosis fungoides* might possibly be mistaken for early nodular leprosy, and *leucoderma* is not infrequently associated with leprosy in the popular mind. It is extremely common, especially in India, and in negro races, and unfortunate sufferers are sometimes to be found in leper asylums. Depigmentation in the leucoderma, however, is more complete and sensory changes are absent. *Lupus vulgaris* is very likely to be mistaken for leprides, and in both diseases acid-fast bacilli are difficult to demonstrate. Lupus evinces a greater tendency to scar formation and there are no sensory changes.

Cutaneous leishmaniasis and, in South America, *espundia*, may be mistaken for leprosy. The lesions on the skin of the face tend to concentrate round the mouth and nose and form a more raised margin than those in leprosy. Demonstration of the Leishman-Donovan body will always settle the matter, but leishmanial lupus-like lesions on the ears may cause difficulty (*see* p. 175). *Acrodynia*, burns and other injuries may leave behind anæsthetic scars.

Neural leprosy has to be differentiated from *syringomyelia*, in which analgesia and loss of heat sense are accompanied by retention of sense of touch and normal sweat function. The absence of nerve swelling and tenderness is important. The nerve injuries caused by *cervical rib* may possibly be called into question, but can be settled by X-ray examination. *Raynaud's disease* has been confused because of trophic changes; *hypertrophic interstitial neuritis* (Dejerine-Sotta's disease) may cause confusion; this is a rare condition with thickening of nerves which may be so great as to render them conspicuous, and is accompanied by sensory and trophic changes, as in neural leprosy, and ultimate production of claw hand. *Von Recklinghausen's disease* (neurofibromata) may sometimes resemble leprosy.

Prognosis.—Leprosy may sometimes be a slight passing ailment, or may become the most repulsive loathsome disease known to man. The two important factors are concentration and distribution of bacilli in the body and resistance. Prognosis is more favourable in the neural than in the lepromatous type. The maintenance of a high standard of general health constitutes a most important element in prognosis. Some patients, even with advanced nodular lesions, are known to have partially recovered. On the whole, the earlier a patient comes under treatment the more favourable the prognosis. On account of the ease with which improvement in muscular power and in sensation can be determined, it is usually easier to assess the progress of the neural than of the lepromatous type. Very spectacular changes are most often seen in patients with tuberculoid lesions.

The danger of contact.—The factors which predispose to the danger of contact are closeness and duration, the infectivity of the case, combined with the age and general health of the person exposed to contagion. A child may acquire the disease after even slight contact.

Recovery.—In early neural cases progress may be stayed or arrested with little or no deformity. But there is no acid test of absolute recovery, and it is said that in such an arrested case, some severe intercurrent disease may herald return of leprosy. From the patient's viewpoint the main thing is whether there will be permanent deformity.

Causes of death.—Leprosy differs from tuberculosis in its low mortality. As a rule the victims do not die of leprosy so much as from intercurrent disease. They die from complications or as the result of crippling deformities. Death may be due to asphyxia from obstruction of the larynx or trachea, or to prolonged lepra fever.

Technique of the lepromin (Mitsuda) **test.**—Material is obtained by removing large, soft, nodules which are boiled in water for 20 minutes and divided into fine fragments with scissors. The epithelium is then removed and the material dried for a few hours with an electric fan, then in a vacuum desiccator over pure sulphuric acid. The dried material is ground up to a fine powder in a glass mortar and stored in a desiccator. In preparing the suspension 0·4 grm. of the dried powder is ground up with 10 c.c. of saline and the fluid pipetted off, a process which is repeated three or four times. Carbolic acid (0·5 c.c.) is then added and made up with normal saline. The suspension is made up in 1 c.c. ampoules, sealed and heated at 120° C. for half an hour. Standardization is difficult.

A series of intradermal tests with full strength lepromin are made in dilutions of 1 in 2, 1 in 4, 1 in 8. Stronger suspensions, as a rule, give stronger reactions. A standard smear is made and the number of bacilli estimated. The skin on the inner aspect of the arm is chosen, the customary dose being 0·2 c.c. The injection must be made intradermally; a slight serous effusion follows it, but disappears after a few days.

In positive cases a nodule appears at the site of inoculation between the first and third weeks, increasing in size up to a maximum. The degree of reaction is read by measuring the size of the nodule by a sliding calliper. In strong reactions there may be slight necrosis. In healthy adults not infected with leprosy the nodule is 6–10 mm. but in resistant cases it is much larger. The lepromin reaction is of use as a means of testing natural resistance to leprous infection.

The iodide test.—This test is of value in assessing the infectivity of cases when repeated bacteriological examinations of skin and nasal mucosa have given negative results. It should only be used, however, when the general health is good and when the blood sedimentation tests are within normal limits. A single dose of 2 grm. of potassium iodide in a glass of water is given at night. This may cause appearance of new cutaneous lesions or efflorescence of old ones, pain or tenderness of the nerves, pyrexia and increased sedimentation rate. The skin and nasal mucosa should then be examined for *Myco. lepræ.* If any reaction occurs, the next dose of potassium iodide should be delayed until it has subsided. If not, increasing doses of 4, 6, 8, 12, 16 grm. should be given at fourteen-day intervals, always with plenty of water. Should no further reaction occur, the leprotic infection may be regarded as arrested.

Treatment of leprosy.—*Chaulmoogra,* or *hydnocarpus oil,* has for a long time been employed as a remedy for leprosy in India and other countries. It is derived chiefly from the seeds of *Taraktogenos kurzii* (Assam and Burma), *Hydnocarpus wightiana* (South-West India), and *H. anthelmintica* (Siam and Indo-China). In recent years hydnocarpus trees have been introduced into Nigeria, the Congo, Fiji and East Africa. In Brazil a somewhat similar oil is obtained from *Carpotroche braziliensis* ("*Sapucainha*"). Though formerly given by the mouth, or by inunction, the more modern method is by injection. The oil itself, when expressed from fresh, ripe seeds of *H. wightiana* and *H. anthelmintica,* is well tolerated, but when stale acquires irritant properties. There is virtually no difference in the composition of chaulmoogra and hydnocarpus oils but, owing to the fact that the latter trees occur in more accessible areas and the seeds are easier to collect, hydnocarpus oil has largely replaced chaulmoogra in the official antileprotic oil of the B.P. (1932).

Sodium hydnocarpate (*Alepol*) (the sodium salt of a selected fraction of the fatty acid of hydnocarpus oil), introduced by Rogers in 1916, is soluble in water and can be given in 3 per cent. solution intramuscularly, subcutaneously and intradermally. If given intravenously it produces endophlebitis and sclerosis of veins.

The ethyl esters were introduced by Macdonald in 1920. Later, it was found that the esters of the total fatty acids of hydnocarpus oil, iodized to make them less irritant, were the most effective. The creosoted oils have been found to be almost as good and are well tolerated when injected.

Hydnocarpus oil and its esters intramuscularly, subcutaneously and intradermally are the most efficacious drugs, but the ethyl esters are more stable than the oil. They should not be exposed to air, but should be prepared and hermetically sealed in ampoules. The use of ampoules is recommended, but when stored in bottles the entire contents should be used on the day they are opened.

Esters must not be reheated. Various theories have been advanced for the action of chaulmoogra oil but none is generally accepted. Possibly it acts by its unsaturation as shown by its high iodine value. Other oils of high iodine value have been tried, amongst them codliver oil, linseed oil, and soya bean oil, but all have given results inferior to those of chaulmoogra.

Antileprol, ethyl ester of chaulmoogra, is dispensed in capsules of 1 grm. and given intramuscularly or by the mouth twice weekly in gradually increasing doses.

Moogrol (Burroughs, Wellcome) is also a mixture of ethyl esters of chaulmoogra, and is given by intramuscular injection. Commencing with 1 c.c. the dose is gradually increased to 6 c.c. at weekly intervals. It has also been given intravenously. The iodized ethyl esters are known as *iodized moogrol* and are usually given by intradermal injection, the leprotic lesion being completely infiltrated by producing coalescing "injection wheals." The dose is 1 c.c., gradually increasing to 5 c.c. It is recommended that tabloids of calcium iodoricinoleate (*Iodicin*) should be given by mouth three times daily, together with moogrol.

The mixture known as *E.C.C.O.* is composed of the ethyl ester of *Hydnocarpus wightiana*, creosote, camphor and olive oil and is given hypodermically in 0·5 c.c. doses, intravenously in 0·25 c.c. Total dosage is 7·5 c.c.

C. E. I. is a mixture of . . .	Chaulmoogra, 50 parts.
	Sulphuric ether, 50 parts.
	Iodine, 0·1 part.

The initial dose, intravenously, in daily injections, is 0·25 c.c., increasing gradually to the maximum, 1 c.c.

Modern workers regard the ethyl esters as less viscid, easier to inject and more rapidly absorbed. On the other hand, the viscidity of the oil is lessened if 4 per cent. creosote is added and if it is injected at 45° C. The oil is more stable and, when stored, is less liable to change, especially after addition of creosote.

Methods of administration.—The exact method—intramuscular, subcutaneous or intradermal—depends upon the type of case and condition of the patient. Intramuscular injections are preferably made into the gluteus maximus; each dose should be divided, and not more than 1 c.c. injected at any given point. Divided injections are given partly by withdrawing the needle and reinserting at a different angle. By warming the oil, injecting slowly, and dividing the dose, painful indurations and abscesses may be avoided. Subcutaneous injections are made beneath lesions occurring on the more fleshy parts of the body, especially the extensor surfaces. The intradermal method, now much used, has the advantage that, in addition to the general effect, there is local action on the area infiltrated. This method is particularly suitable for the tuberculoid lepride. Two techniques are generally employed:

(1) The "plancha" method, used by American workers in the Philippines, by which multiple small fractional doses (0·05—0·1 c.c.) are injected intradermally, a small wheal about 5 mm. in diameter being raised round each puncture. By this method an area of 12 sq. cm. or more is infiltrated at one sitting by a short needle which enters the skin for 2–3 mm.

(2) A long thin needle is threaded through the skin to its socket, and the oil or esters injected as the needle is withdrawn. A successful injection should leave behind it a long wheal along the needle track, but there should be no re-infiltration of a skin area for one month, or at least until all induration produced by the last injection has resolved.

Doses.—Tolerance to hydnocarpus oil varies with weight, age and general condition. It is necessary to remember that each injection produces a negative phase of varying duration. The better the physical condition, the larger the doses the patient will tolerate. In estimating tolerance the blood sedimentation rate is important. The customary dose of the oil, hydnocarpate (*Alepol*) or esters, is from 0·5–6 c.c. once or twice weekly though occasionally doses up to 30 c.c. per week have been employed. It is usually administered as a 3 per cent. aqueous solution, commencing with 1 c.c., and rising by 0·5 c.c. to 5 c.c. In many cases it is better to give a proportion intradermally and the balance by other methods.

Special treatment should be continued until all active signs of the disease have disappeared, repeated bacteriological examination of skin and nasal mucosa are negative, and the nerves are no longer thick and tender. When active signs have definitely disappeared the disease is said to have become "quiescent," but when this state has remained stationary for two years it may be said to have become "arrested."

Special treatment aims at the destruction of *Myco. lepræ*; when they have practically disappeared from the body, the deformities can be relieved, but sensation can never be restored in permanent lesions. Compulsion is out of the question and patients must co-operate willingly. They should be encouraged to come as early as possible, and should be warned from the onset that treatment must necessarily be protracted.

Lepra reaction.—If this reaction occurs during the course of intensive treatment the injections must be stopped, but if there is some complicating disease (such as malaria) this must be specifically treated. During the lepra reaction the patient should be confined to bed and the bowels freely evacuated. Alkalies are advisable: 60 gr. of *sodium bicarbonate* may be given four times daily. Intravenous injection of potassium antimony tartrate, $\frac{1}{3}$ to $\frac{1}{2}$ gr. three times weekly, has proved an effective desensitizer. Intravenous injections of mercurochrome (3 c.c. of freshly made 1 per cent. solution) may sometimes control the condition. Calcium lactate and calcium gluconate in large doses act as adjuvants. Intravenous injections of aniline dye—trypan blue and methylene blue—have also been employed.

Treatment of pain.—Pain is usually associated with the lepra reaction, and there is increase of pain and tenderness in the distribution of affected nerves. For this, adrenalin hydrochloride 1 in 1000 solution (0·2–3 c.c. in 5 c.c. saline) is infiltrated into the perineural tissues, or alternately 0·02 grm. of ephedrine sulphate (dissolved in 10 c.c. of a 0·5 per cent. sodium bicarbonate solution) given by the mouth or injected similarly round the nerve usually gives relief. Snake venom in small doses has also been found useful. In leprous neuritis, with œdema of hands and feet, aneurin (vitamin B_1), in 10 mgm. doses daily, is said to be successful.

Surgical treatment.—*Excision of lesions.*—If there is only one small skin lesion, say less than 1 inch in diameter, it should be excised. Large outstanding nodules should be shaved off, the base being touched with strong carbolic or nitric acid. The electric cautery or carbon dioxide snow have been similarly employed. The treatment of perforating ulcers is a difficult problem. Necrosed bone should be removed. Chronic ulcers with indurated margins may be stimulated by infiltration with hydnocarpus esters, and by applying sulphonamide powders or paste. Amputation is seldom necessary.

When the thickened ulnar nerve is constricted by dense fibrous tissue behind the condyle, or the peroneal nerve is bound to the head of the fibula, the thickened band may be severed. The nerve sheath may be slit with benefit.

The eye.—If there is involvement of the iris, mydriatics (atropine) must be instilled to prevent further fixation. Particular care must be taken in the general treatment to avoid reactions which have an adverse effect on the eye. It is said that infiltration of the bulbar conjunctiva with a 1 in 1000 solution of trypan blue relieves the pain and congestion. But the best permanent results are obtained from improvement in the general health.

When there is anæsthesia of the cornea, paresis of the lids, or ectropion, the eyeball has to be protected with liquid paraffin, and a cotton-wool pledget should be tied over it at night. Sometimes the condition may be improved by marginal tarsorraphy.

The nose.—Special treatment is often required for the nasal ulceration, The crusts should be removed and the mucous membrane anæsthetized with cocaine and adrenalin or some caustic, such as trichloracetic or chromic acids (1 in 10 solution), applied and fulgurated with a diathermy apparatus. Sometimes douching with 2 per cent. sodium bicarbonate solution and painting with iodized hydnocarpus esters is also useful. For offensive discharge the following nasal lotion is used :

℞.	Sodii chlorid.	*aa* gr. 22 (1·42 grm.)
	Sodii bicarb.	
	Pot. chlor.	ʒ 2 (7·78 grm.)
	Calc. phosph.	℥ ½ (15·5 grm.)

Sig.: ½ oz. to be used with ½ pint of water as a nasal douche.

Deformation of hands and feet.—Rehabilitation measures, such as carefully planned exercises, can often lessen deformities. The necessary movements may be produced in agriculture or textile industries, as carried out in the model Culion Island Colony in the Philippines.

Trophic ulcers.—Cochrane advocates filling the cavities with 5 per cent. sulphonamide paste, bandaging or strapping and leaving for one week. The following is recommended :

Sulphonamide (Sulphapyridine)	gr. 75 (5 grm.).
Adeps lanæ	ʒ 18 (70 grm.).
Liq. paraff.	ʒ 6½ (23 c.c.).

Operative procedures are sometimes necessary. Metatarsalectomy is advocated. The limb should be devasculated by a tourniquet, and the bone disarticulated before removal. Local anæsthesia, adequately given, suffices, and the tourniquet should not be removed until the wound has been well packed with sulphonamide paste and a tight bandage applied.

Subsidiary measures.—The production of protein shock by intravenous injections of milk or other forms of protein sometimes causes temporary improvement and aids in healing up intractable ulcers, but must be used with caution. The grounds on which these methods are based are the favourable results which sometimes follow febrile reactions in leprosy. Row in Bombay recorded such improvement after weekly subcutaneous injection of carbolized cultures of tubercle bacilli. Intravenous injections of killed *Bact. coli* (*pyrifer*) raise the temperature and cause a reaction, and good temporary results have followed the similar use of typhoid-paratyphoid vaccine in graduated doses, commencing with 50 million and gradually increasing to 200–300 million organisms in order to obtain satisfactory reactions.

Somewhat analogous results have been recorded from time to time by autogenous vaccines made from ground-up lepromatous material, and other acid-fast organisms grown from leprous nodules. The so-called anti-lepra serum of Rienstierna was obtained by injecting such a culture into sheep. Rapid and favourable action has been claimed by some observers as a result. X-rays and radium have also been tried, and various baths, such as iron, copper sulphate and iron arsenical baths at a temperature of 110° F. (in Java).

Some mention must be made of the recently-developed sulphonamide (promin) in treatment (Dinan, Pogge and others, 1943). This is the best of all preparations so far tried and has given encouraging results. The oral administration is toxic, and larger doses are tolerated by the intravenous route. By this method 1–5 grm. are injected daily for six days a week. The majority of cases have received the larger dose for months, with short intervals of one to two weeks three times yearly. The concentration in the blood declines rapidly, only traces being found 6–8 hours after injection. The toxic effects are anæmia in 46 per cent. after six weeks. The blood must therefore be watched, but responds to liver and iron preparations. Leucopenia was noted in 3 per cent. Allergic dermatitis and rhinitis may ensue. There is no evidence of any bactericidal action. After a year's treatment in 22 cases, 15 were definitely improved. Promin acted favourably on leprous keratitis, iridocyclitis and ulcers.

Prophylaxis.—If children could be prevented from coming into contact with infectious cases then the number of adults who would later become victims would be so few that the leprosy would decline. In planning preventive measures the incidence of child infection and of infectious lepromatous cases should be ascertained. If the former should reach 25 per cent. of the total and 20 per cent. of the latter, then intensive preventive measures must be undertaken.

The patients must be segregated in special areas near villages connected with a properly equipped centre. Infective cases in towns can be isolated solely in institutions. General hospitals should be prepared to treat leprosy in out-patient centres set apart for this purpose. Special research units should be developed, and special measures instituted for the care, segregation and observation of children with leprosy. Propaganda and carefully planned special training are essential.

A model leper colony is situated on Culion Island in the Philippines. It is a town with laundries, theatre and schools where some 8,000 lepers were originally segregated ; at the end of ten years the numbers had been reduced to 3,000 by natural causes and almost complete cessation of new infections.

Since improvements have been made in the dietary, and intensive treatment has been given with ethyl esters of chaulmoogra, especially good results have been obtained in children.

In no country should lepers be permitted to beg in the streets, keep shops, or handle food.

CHAPTER XXXII

YAWS (FRAMBŒSIA)

Synonyms.—Pian; Frambœsia; Boubas (Brazil); Coko (Fiji); Parangi[1] (Ceylon); Dube (Gold Coast); Purru (Malaya).

Definition.—Yaws is a contagious inoculable disease, characterized by primary sore and indefinite incubation period, followed usually by fever, rheumatic-like pains, and the appearance of papules which generally develop into a fungating, encrusted, granulomatous eruption. Running a chronic course, it usually protects against a second attack. The disease is caused by *Spirochæta pertenuis*, and is controlled by salvarsan and bismuth salts. The organisms of yaws and syphilis are indistinguishable and the lesions produced are extremely difficult to differentiate.

History.—The first descriptions, by Oviedo, of what we know as yaws did not appear until the sixteenth century. Before this period allusions in the literature appear to be mere surmises. Deductions from historical records suggest that yaws is of more ancient lineage than syphilis. It is clear that what we now know as syphilis appeared with dramatic suddenness at the end of of the fifteenth century and, as a new and devastating disease, spread rapidly over Europe. According to records, the disease broke out after the return of Columbus to Spain. Oviedo (1478–1557) was in Barcelona at the time, and in his *Historia General y Natural de las Indias*, he stated that it was contracted from Indian women by the Spaniards who accompanied Columbus, that it was brought by them to Spain, and transmitted to the army of Charles VIII. Las Casas (1474–1556), in his *Historia de las Indias*, refers to a disease which was very dangerous to Spaniards, and was known as syphilis, being known in Italy as the "French malady." Dias de Isla, a physician practising in Barcelona in 1493, gives a very complete account and states that it was unknown before that year, and that it was brought by the crew of Columbus on their return from the *first voyage* to Haiti. Dias himself treated several sailors from the squadron, including the pilot, Pinçon of Palos.

In the autumn of 1493, Charles VIII of France invaded Italy with a rabble army. He captured Naples on February 22, 1495, but a new plague (syphilis), accompanied by severe skin lesions, broke out and necessitated the evacuation of the city. The spread of syphilis can be traced, according to Pusey (1933), with the dispersal of Charles's army throughout Europe. In 1497 it reached England and Scotland. In Japan it was not recognized till 1509 at Nagasaki, where it was attributed to Chinese and Portuguese sailors.

Syphilis, when introduced into a non-immune population, as in Uganda, in the nineteenth century, reproduced symptoms and manifestations recorded by our ancestors in the fifteenth; under these circumstances there is little doubt that syphilis can act as a devastating epidemic. According to the far-reaching researches of such authorities as Virchow (1896) and Elliot Smith (1930), no syphilitic bone of pre-Columbian origin has been discovered. On the other hand, Means (1925) and Williams (1932) have found the long bones of Indians showing evidences of syphilis in primitive races in North and South America; and the former found evidences of it in skeletons of the prehistoric mound-building Indians of Ohio.

---

[1] This word means "foreigner," a term applied by the natives to the European invaders of Ceylon.

It is known that yaws often occurred in epidemic form on board slave ships and it may well be that the disease has an African importation into the New World. Much has been written of the possible identity in former times of such diseases as the " button scurvy " of Ireland, " sibbens " of Scotland and " radesyge " of Norway and Sweden. It may well be that during the seventeenth and eighteenth centuries they represented a severe form of syphilis.

Recent views on the syphilis-yaws question.—In Jamaica, Turner, Saunders, and Johnson record that no cardiac disease has been encountered in yaws cases, and this has been confirmed by radiographic examinations. In their critical survey of yaws in that island, they brought forward several new points. The " attack rate " in adults is as great as in children, and yet nothing like congenital syphilis has been seen in Jamaican babies, and this is held as strong evidence against the identity of syphilis and yaws. Infants and children in Jamaica are more liable to infection than are adults, and 90 per cent. of cases contract the disease before they are fifteen years of age.

It may well be that yaws and syphilis have sprung from a common ancestor. In yaws it is probable that the spirochæte, under the more primitive conditions of the tropics, has spread from man to man by intimate contact, whilst the syphilitic spirochæte under more civilized conditions, where such contact is not possible, came to be communicated by the venereal route, thereby assuming a more virulent character and evolving (as do certain other spirochætes) neurotropic strains. Intermediate forms between the two classical forms of these diseases, which are so closely related as to be zoologically referable as " sub-species," undoubtedly have become evolved in time, as in the non-venereal childhood syphilis of the Arab tribes of the Euphrates and Iraq, known as " Bejel " (Hudson). This disease has been well described in Deir-ez-Zor in Syria, where there is a high incidence of syphilis but very little gonorrhœa. This syphilis is spread by personal contact, is of low virulence, gives a positive Wassermann reaction, and corresponds to the endemic syphilis of Asia Minor described by von Düring. The most frequent lesions are in the mucous membranes of the mouth ; but in other respects—in the special affinity for children, and in the production of hyperkeratosis and depigmentation—it resembles yaws, and circinate lesions of the soles of the feet, resembling crab-yaws, are common. Depigmentation of the dorsum of the hands resembles that described by Lacapère in Morocco, but Hoff and Shaby state that meningo-vascular lesions may still be observed amongst these peoples.

Geographical distribution.—Yaws is common in tropical Africa, West Indies, Ceylon, Pacific islands, Papua, the East Indies, and the Malay States. In India and China it appears to be rare. Children in the West Indies and Fiji are especially liable. During recent years it has become extremely prevalent in Kenya Colony, Tanganyika Territory, and Uganda, where it is spreading with great rapidity. On the other hand yaws has disappeared to a great extent from Guiana, Ceylon and Barbados, where it was previously extremely rife.

Epidemiology and endemiology. *Contagion and heredity.*—As yaws is highly contagious, all circumstances favouring contact with the subjects of the disease favour it. Simple skin-contact does not suffice ; a breach of surface is necessary. The knowledge that the secretions from yaws lesions could transfer the disease to another person was well known to the slaves of the West Indies, and they practised auto-inoculation in their children who did not show a generalized eruption.

The disease frequently commences in a pre-existing ulcer, the organism (spirochæte) being conveyed by flies to the previously lacerated surface (p. 978). Cases originate in certain dirty houses, the virus from previous yaws patients seemingly impregnating the floors and walls of the filthy huts. In this manner the disease may be, and in some cases no doubt is, acquired without direct transference from an existing case. In some countries, as in Ceylon, yaws is a disease of the flat, low-lying districts, while practically absent from the hill country; in Assam, on the other hand, it is more common among the hill tribes than among dwellers of the plain. Ramsay has shown in Assam that native hill people, who only exhibit obscure lesions, such as condylomata, while living at high altitudes, develop florid yaws when they come down to the plains. In Jamaica, Saunders and Kumm have emphasized the importance of rainfall and geological formations on the distribution of yaws. Wherever there is porous limestone there is little or no yaws.

Yaws is neither hereditary nor congenital. A pregnant mother suffering from yaws does not give birth to a child suffering from the disease, nor one which will subsequently develop yaws, unless the virus be first introduced directly through a breach of surface after birth. It is not conveyed by the milk; nor does a suckling suffering from yaws necessarily infect its nurse.

This statement should be qualified by the well-known fact that a syphilis-infected mother does not inevitably transmit the disease to her offspring, and if she does transmit, she may do so irregularly, not to one child, but to the next, and to one only of twins.

Although two-thirds of the cases in the West Indies, Pacific Islands and Ceylon occur before puberty, no age is exempt. In Jamaica the peak of the infection rate is about eight years. No new infections are found after thirty. Three males appear to be infected to every one female. It has been frequently remarked that yaws shows a predilection for certain native races. On the whole, the negro and negrito stock is specially liable to severe attack.

Yaws at the present day shows a striking limitation to the tropics, but it is a disease so readily communicable by direct contact that it seems remarkable that it does not spread in temperate regions. In the tropics yaws is limited to low level areas, and to rural districts with primitive sanitation. In Haiti, for instance, yaws is the disease of distant villages, and syphilis with chancre is common in the main town. In the Philippines the same is true: in the country, yaws; in Manila, syphilis.

Ætiology.—In 1905 Castellani demonstrated in scrapings of yaws tissues an extremely delicate spirochæte—*Spirochæta pertenuis*—very like that of syphilis. To demonstrate this spirochæte, slides should be prepared from scrapings of an incised yaw papule before it has ruptured. The films may then be stained with Giemsa, or made by the indian-ink method; better still, the living parasites may be detected in fresh undried films by darkground illumination. A fully developed yaw is unsuitable, because it has been exposed to external sources of contamination and a variety of organisms will be present and may confuse the observer. Dobell and others have been unable to distinguish any structural differences between this spirochæte and *S. pallida* of syphilis (Fig. 228, 5, p. 864).

S. pertenuis has been found in the spleen, lymphatic glands, and bonemarrow; doubtless it also occurs in the blood. It is inoculable into monkeys and rabbits; in the former, especially in the orang-outang, it gives rise to lesions similar to those in the human subject.

Cultivation of *S. pertenuis* was successfully performed by Noguchi in ascitic fluid containing a piece of fresh animal tissue, such as the kidney, the whole being covered with a layer of sterile paraffin. This rather complicated technique has been simplified by the later work of Hata, who substituted horse-serum, the inoculation being made through the upper solidified layer. Strict anærobiosis is necessary.

Kumm has brought forward strong evidence that in Jamaica, at any rate, a minute fly, *Hippelates pallipes*, carries the spirochæte from one person to another. He collected the flies at the rate of 5,000 per hour from one ulcer; they crawl under the scab and ingest large numbers of *S. pertenuis*, which are afterwards regurgitated. *H. pallipes* is an oscinid fly having peculiar mouth-parts, with projecting spines on the pseudotracheæ and labellæ (*see* p. 985).

Inoculation into monkeys.—The most extensive and minute observations of Schöbl on *Cynomolgus philippinensis* with emulsified extracts of yaws lesions containing *S. pertenuis* deserve mention. The injections were made on the nose, eyebrows and scrotum. From three to five weeks after inoculation, papules appeared, corresponding to the typical yaw. Later, they spread peripherally like the ring-worm form of this disease. The disease in the monkey on first inoculation runs its course without developing into diffuse secondaries, but generalized yaws is produced by superinfection. Other late manifestations, such as lupus-like ulcerations and keratoderma of plantar surfaces, resemble those seen in man.

Human inoculation.—The fact that the disease could be transferred by secretion from yaws lesions was well known to the slaves in the West Indies. Charlouis and others have inoculated yaws patients with syphilitic virus and have produced a chancre at a site of inoculation. Schöbl considers that *S. pallida* is panblastotropic with a tendency to invade and multiply in all tissues and produce lesions, but is mesoblastic in its tendencies. Syphilitic lesions are found in the skin, mucous membranes, bones and muscles, viscera and nervous system. The spirochætes invade the cardio-vascular system and enter the placenta, giving rise to congenital syphilis. The yaws spirochæte is epiblastotropic, invading certain tissues, particularly the skin and bones; the nervous and cardio-vascular systems are not usually invaded and the disease is not congenital. It is suggested that in the few instances in which lesions of the internal organs and cardio-vascular system have been reported, co-existing syphilis has not been rigidly excluded.

Yaws, moreover, shows a striking limitation to the tropics, and the effect of climate upon it is such that it does not spread in temperate climates from cases which are introduced. It is more common at low altitudes and in areas with higher rainfall.

Yaws spirochætes are unable to penetrate unbroken skin surfaces. Auto-inoculation may occur during the early course of the disease in man; the infection may spread to other parts of the skin, but mucous membranes are not invaded.

Other animal inoculations.—Nichols originally showed that yaws, like syphilitic lesions, can be produced in the testis of the rabbit, though the incubation period is shorter. Pearce and Brown observed, in intratesticular inoculation with *S. pertenuis* in the rabbit, a granular and finely nodular periorchitis, a lesion different from that of *S. pallida*. Turner and Chesney in Haiti found that in rabbits injected with *S. pertenuis* the testicular lesions consisted of miliary granules in the tunica and epididymis, but that general enlargement and induration (so common after inoculation with *S. pallida*) do not occur.

Pathology.—A feature of yaws lesions is the great thickening of the epidermis and degeneration in the epithelial cells. In later stages there may be hyperkeratosis. The elongated papillæ are vascular, and are infiltrated with lymphocytes; leucocytes and plasma cells are also numerous. In contrast with syphilis, perivascular infiltration in the corium is absent, and there is no endarteritis as in syphilis. Dupont and Dubois describe the primary lesion as an epidermic papule of which the centre becomes necrotic and leads to ulceration. Cellular infiltration is limited. In contradistinction, the syphilitic chancre erodes the

epidermis and extends more deeply. In secondary yaws large papules are formed by inflammatory infiltration with hypertrophy of the epidermal ridges. In the gummatous stage the essential feature is dominance of the epithelioid elements in the infiltration.

Symptoms.—As in syphilis, the symptoms of yaws can be divided into three stages—primary, secondary, and tertiary.

PRIMARY LESION (*madra buba* or "mother yaw").—According to Sellards the *incubation period* in experimentally-inoculated yaws in man is three and a half to four weeks; in experimental apes it may be as long as three months. Naturally-acquired yaws is reputed to have, as a rule, a longer incubation period than the inoculated disease. The primary lesion may appear as a granuloma or a papule at the site of inoculation, 1–7 cm. in diameter, and is known as the "frambœsoma." It may develop at the site of some old skin lesion. It is ordinarily extragenital, but may be situated on any part of the body: the buttock, thigh, knee, leg, arm, breast, or lip (Fig. 90), but is rare on the scalp. The lower part of the leg is the site of predilection; the breasts of nursing women and the mouths of suckling babies are not uncommon sites. In Moss and Bigelow's large series the genitalia were the seat of the primary lesion in only 1 per cent. In native women it is frequently observed at the bend of the elbow, or on the hip, and is contracted in this situation from carrying children who are infected with the disease. The primary lesion may be so small as to escape detection; it may be single or multiple, and, in fact, great difficulty may be experienced in differentiating it from allied cutaneous lesions, but, as a rule, it is remarkably persistent, lasting from two to four months, and it may persist for a year or more.

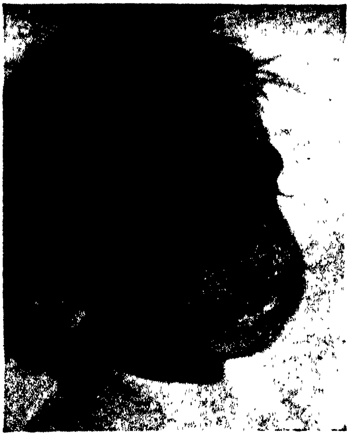


Fig. 90.—Primary yaws sore on lips of Australian aborigine child. (*Dr. H. Basedow, Adelaide*)

According to the Jamaican Yaws Commission, the primary lesion is found on the lower extremities in over 70 per cent. of cases. In 39 cases it was found:—

On head, face and neck	in	1
On upper extremities	„	4
On genitalia	„	1
On leg	„	12
On ankle and foot	„	21

The lesion, on becoming larger, becomes covered with a yellowish secretion or scab. It is at this stage known as the "mother or master yaw," the "mama pian" of the French. In ordinary locations yaws lesions are not painful, unless firmly pressed.

The appearance of the lesion is preceded by a certain amount of constitutional disturbance. The intensity of the general symptoms varies within wide limits; sometimes they are hardly perceptible, so are not complained of, but usually there is well-marked malaise with rheumatic pains. Occasionally there is severe constitutional disturbance lasting for about a week, with rigor, smart fever (100° to 103° F.), persistent headache, pains—worse at night—in the long bones, joints and loins, and sometimes gastric disturbance and diarrhœa, especially in children. The lymphatic glands in the immediate vicinity become enlarged. During the decline of these constitutional symptoms the secondary eruption appears. The Wassermann reaction becomes positive three to four weeks after the primary lesion and rapidly grows stronger in titre.

Secondary stage.—This is ushered in by a fine, light-coloured furfuraceous desquamation. The skin becomes harsh and dry, loses its natural gloss, and here and there patches of desquamation (best appreciated with the aid of a hand lens) are formed. These patches are mostly small and circular; occasionally they are oval, irregular, or form rings encircling islets of healthy skin scattered irregularly over limbs and trunk; sometimes they are almost confluent, the patches coalescing and making the skin look as if it had been dusted over with flour. On the other hand, this furfuraceous desquamation may be so slight as to be overlooked. In some instances the heaping-up of desquamating epidermic scales produces white depigmented patches, very evident on the dark skin of a negro or oriental.

This patchy, furfuraceous condition of the skin may persist throughout the attack, or may reappear as a fresh eruption at any time in the course of the disease. It has been described by Schöbl and Sellards as "keratoid exanthem" in artificially-inoculated yaws.

Appearance of the yaw (Fig. 91).—When the furfuraceous patches have been in existence for a few days, minute papules appear in them. This very characteristic eruption, from which the disease takes one of its names—*frambœsia* (or *raspberry*)—breaks out three months after the primary lesion. These secondary lesions may vary in size from a pin's head to half a crown and, according to Spittel, begin around the primary sore ("mother and daughter yaw"). The itching is usually considerable. As in syphilis, the eruption may be very pleomorphic; it may be roseolar, or consist of macules with desquamation resembling a squamous syphilide. It may appear on any part of the body, especially in exposed situations and on the anterior surface. The papules occur in groups, the larger appearing to be surrounded by a group of satellites, which has given rise to the various native designations for yaws. Auto-inoculation is probably responsible for the appearance of these lesions in symmetrical fashion, whenever the skin or mucous surfaces come into intimate contact; they are present at the angles of the mouth, in the axillæ, in the anal cleft, and in the inguinal region; in contradistinction to syphilis, they are rarely present on the true mucous surfaces, but often in clusters inside the nostril. Several of the groups may coalesce to cover a surface.

The yaw is pushed up from the rete Malpighii through the horny epidermis, which breaks over the summit and splits in radiating lines from the centre, the necrosed segments curling away from the increasing papule. Soon a yellow point appears around a hair follicle, consisting of a cheesy-looking substance which cannot be wiped away, unless undue force is used.

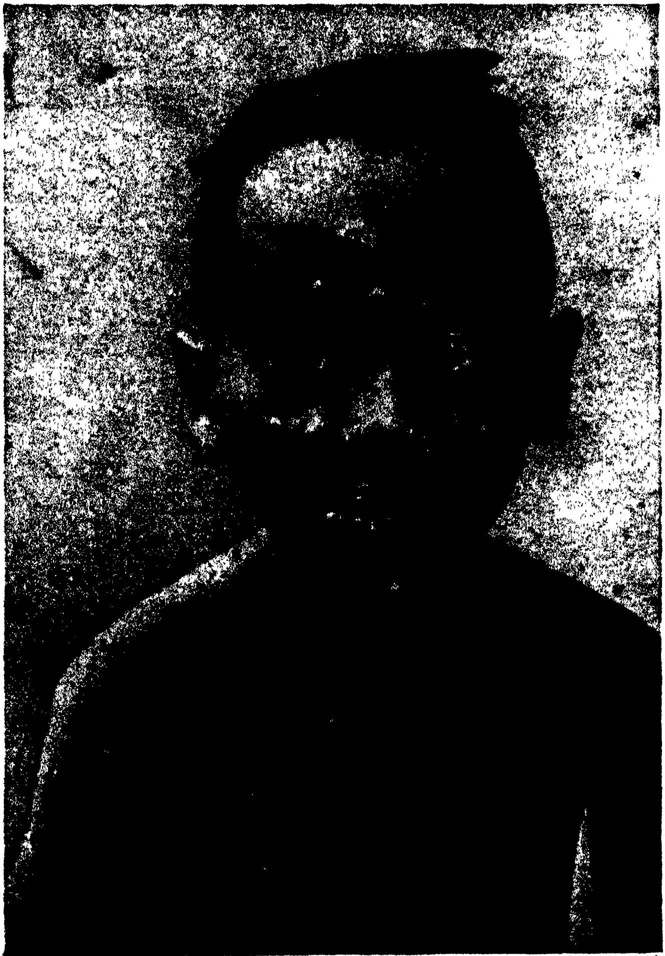


Fig. 91.—Secondary yaws in a Malay boy. (*W. E. Le Gros Clark.*)

From this stage the papule may either cease to grow, the apex becoming depressed, or may go on to form the typical yaw. In the latter case the lesion gradually grows into a rounded excrescence, the yellow material at the top widening out so as to form a complete cap encrusting the little tumour. The smaller tumours are hemispherical; the larger are more flattened, or even depressed at the centre, possessing everted, somewhat overhanging, rounded edges. Occasionally, though rarely, a big yaw may include an area of sound skin.

The firmly adherent crust which caps and encloses an uninjured yaw is yellowish, granular, blotched with blood-stains and encrusted dirt. Deprived of its crust, the little swelling is seen to be red, generally smooth and rounded on the surface, and oozing pale yellowish serum in which spirochætes may be demonstrated ; when inspissated, this serum forms a fresh cap to the yaw, and on microscopic examination is found to be teeming with the organisms. According to size, it stands out anything from ⅛ to ¾ in. above the surrounding healthy skin. Pus, unless a consequence of irritation, is not, as a rule, found under the crust.

Although the formation of the papules and yaws is attended with much itching, the yaw itself is not at all sensitive ; the tumour may be touched, with acid even, without causing pain—a diagnostic point of some importance. Sometimes, as in syphilis, the eruption has a circinate character, the so-called " ringworm yaws." The itching of yaws lesions is a point of differentiation from syphilis, but, as Blacklock has pointed out, native races are exposed to insect bites and dirt.

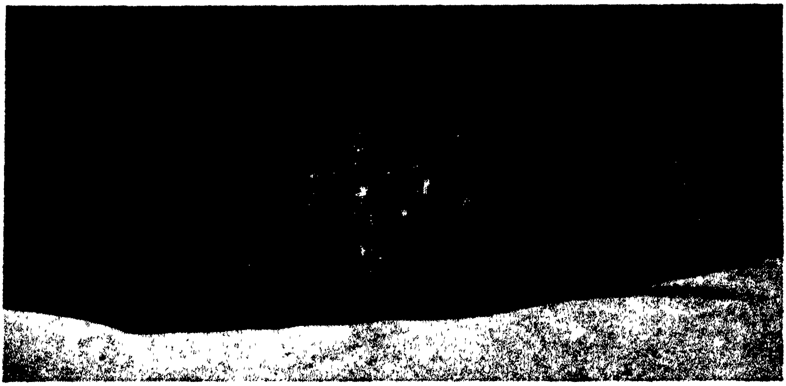


Fig. 92.—Tertiary yaws ulceration on forearm of European.

The yaw usually attains its maximum development in two weeks. For several weeks longer it remains stationary before beginning to shrink. The crust then thins, shrinks, darkens, separates at the periphery, and at last falls off, disclosing, at the site of the former fungating mass, a slightly thickened spot of fairly sound skin, which, though pale at first, may subsequently become hyperpigmented.

Sometimes the secondary rash takes on a papular appearance, when the lesions are known as " acuminate papules." These are symmetrically distributed over the back, shoulders, arms, elbows and knees, and much resemble a follicular syphilide. Secondary lesions may last from six months to a year. Simultaneously with the eruption, as in secondary lis, there may be a uniform, painless enlargement of the lymphatic s, in the aspirated lymph of which the specific micro-organism may be demonstrated. When the lesions subside, pigmented spots remain, as in secondary syphilis, and are specially noticable on the palms of the hands.

Lichenoid eruptions.—*Lichen frambœsianus* ("*Pian datre*") is a lichenoid generalized eruption of the skin described by Dutch writers in the East Indies. It is a micropapular eruption which is very striking in appearance and is not associated with *yaws papules*. It is, of course, analogous to secondary lichenoid eruptions in syphilis, and must be distinguished from other lichenoid eruptions, such as lichen ruber planus, lichen pilaris and lichen scrofulosorum. It is now generally recognized as an early secondary manifestation in children and young adults, the same condition as has been described by Nicholls as "furfuraceous desquamation" and by German writers as the early frambœsiform efflorescence. The lichenoid eruption is apt to occur in patches over the shoulders and, according to Deibel and Elsbach, there is a tendency to

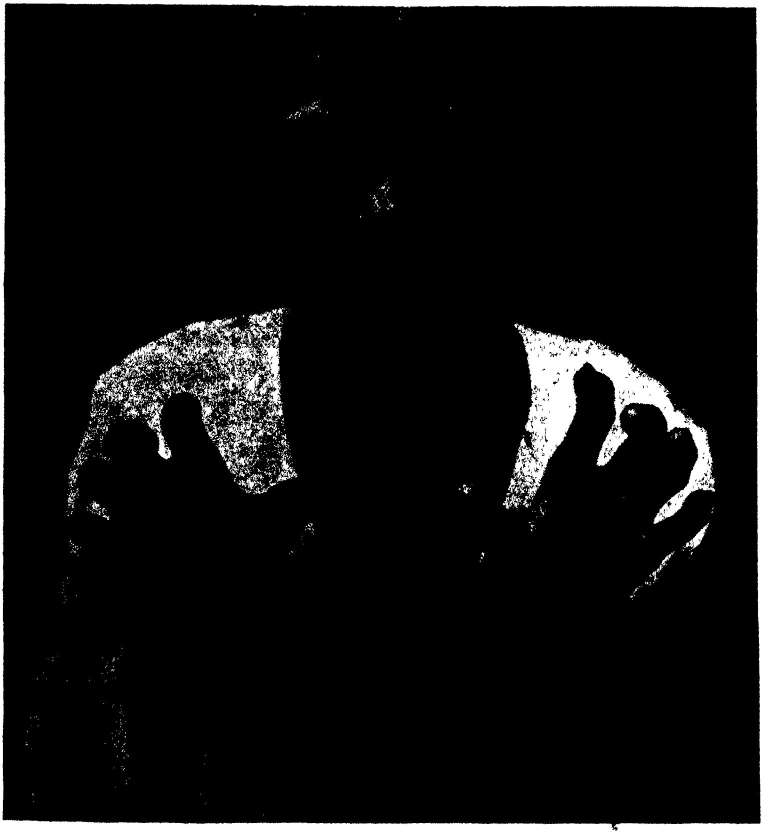


Fig. 93.—Tertiary yaws. Onychia of fingers.

hyperpigmentation of the peripheral micropapules, associated with depigmentation of the centre.

The serum of patients in the secondary stage gives marked positive Wassermann and Kahn reactions, and this makes the differential diagnosis from syphilis impossible by these means.

Tertiary stage.—It sometimes happens that the tumours, instead of becoming absorbed, break down and ulcerate, the ulceration, which may last for years, being confined to the yaw itself. In other instances ulceration goes deeper and extends circumferentially, giving rise to extensive sores with subsequent cicatrical contractions. Such ulcerations occur in about 8 per cent. of cases and may or may not be encrusted.

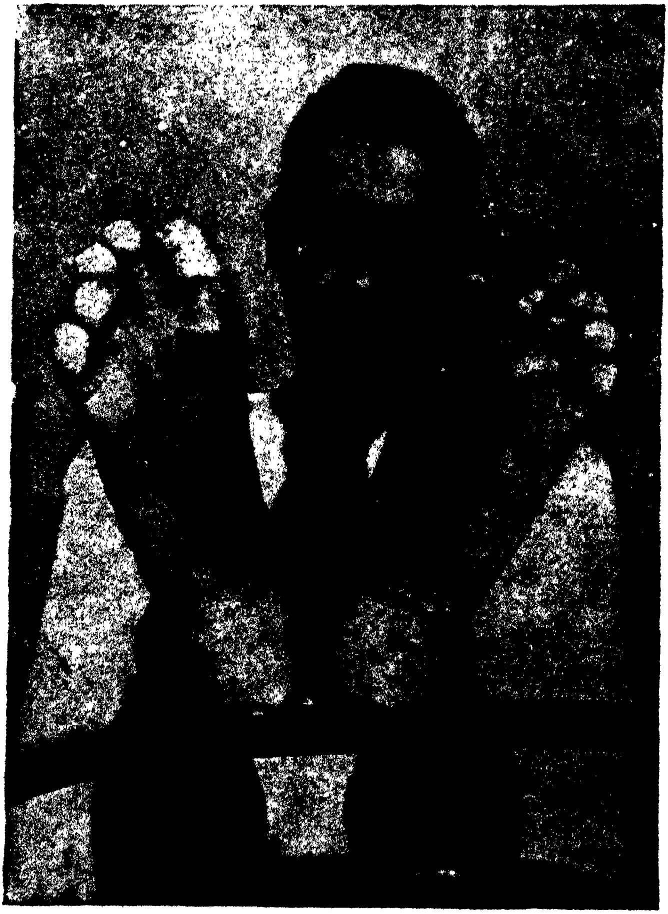


Fig. 94.—Feet yaws, or "crab yaws." (*Dr. J. D. Reed.*)

(Fig. 92.) With the development of the deeper and wider forms of ulceration, the typical lesions of yaws may disappear for a time, or perhaps permanently. In the latter case the ulcers are said to be non-infective. Ulceration of the greater part of the limbs, especially the leg and ankle, may take place. Tertiary manifestations are seldom observed in cases which present late secondary lesions. The serum of these cases gives positive Wassermann and Kahn reactions, but the cerebro-spinal fluid, in cases of advanced ulceration of the nose and other parts of the body, gives a negative reaction with a normal cellular and biochemical picture.

Lesions of the hands.—A scaly condition of the palms of the hands may persist for years. Multiple dactylitis, with uniform swelling of the phalanges, onychia, paronychia, atrophy of the nails, and subsequent deformity, is often observed. (Fig. 93.)

Foot yaws (" Dumas," or pink parangi—Ceylon ; " crabs," or " crab yaws "—West Indies).—When a yaw develops on the sole of the foot it causes much suffering because it is bound down by the dense and thick epidermis. Spreading laterally under the thick, leathery and unyielding epidermis, it may become large. After a time the epidermis over the growth gives way, splitting up in a radiating fashion (Fig. 94). Pressure being thus removed, the yaw fungates, and suffering diminishes. Crab yaws may last a lifetime after infection in childhood. Chesterman suggests that in the foot lesions a fixation point for *S. pertenuis* is formed. A condition known as " clavus " in Dominica results from the healing of these granulomata ; the centre of the core drops out, leaving an irregular erosion of the sole of the foot, or there may be deep fissures or cracks. Similar pitting occurs on the palms of the hands. According to Sayers, this is the commonest lesion of yaws in the Solomon Islands, and causes great disability, especially in children ; when bilateral it incapacitates them from walking.

[redacted]

Fig. 95.—Gangosa in an Australian aborigine. (*Dr. H. Basedow, Adelaide.*)

Gangosa (derived from the Spanish meaning " muffled voice "), or destructive ulcerous rhino-pharyngitis (Fig. 95), which is now generally regarded as a sequel of yaws, usually commences as an ulcer on the soft palate. Slowly spreading, it may make a clean sweep of the hard palate, the soft parts, cartilages and bones of the nose, sparing the upper lip, which is left as a bridge across a great chasm, the floor of which is formed by the intact tongue. A most offensive odour is given off from the ulcerated surface. The disease may be arrested spontaneously at any period of its progress, and long before such extensive mutilation as that described has been effected ; but it is always a longstanding and chronic affair and may linger as an indolent ulceration for years. As a rule, the larynx is spared ; but although phonation may be retained, articulation is seriously impaired. Gangosa occurs at any age, but is rare in young adults, though Leyes states that in Guam he has seen it in children of 3, 4, and 9 years of age. It is very common in parts of the West Indies (Dominica, 60 cases in a population of 2,000), Guam (1·5 per cent. of the population), the Carolines, Fiji, Ceylon, British Guiana, and West, Central, and East Africa. It is often found associated with the bone lesions of yaws.

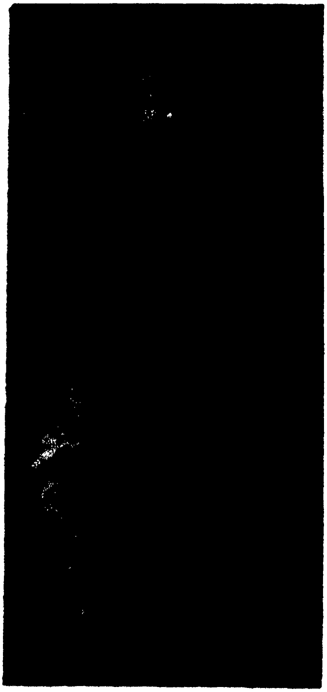


Fig. 96.—Goundou.
(*Dr. P. M. Shepherd.*)

Goundou, or Anákhré (" *Gros Nez* ").—In 1882 MacAlister drew attention to what were termed the horned men of Africa, and in 1887 Lamprey gave further details illustrated with drawings. The natives call the disease goundou and anákhré. Later observations show that it has a wide distribution in Central Africa and South America, and that a similar disease occurs in the larger apes, chimpanzees, and baboons. An ancient Inca skull from Peru, described by Letulle, shows the characteristic lesions of goundou.

Stannus and Hamerton have shown that in the apes the hyperostosis is probably the after-result of osteitis cystica.

Goundou usually commences during childhood, although adults may be attacked. The earliest symptoms are severe and more or less persistent headache which, after a time, is associated with a sanguino-purulent discharge from the nostrils, and formation of symmetrical swellings the size of a small bean at the side of the nose. Apparently the swelling affects the nasal process of the superior maxilla. The cartilages are not involved. After continuing for six or eight months, the headache and discharge subside. The paranasal swellings persist, and continue slowly and steadily to increase until in time they may attain the size of an orange, or even of an ostrich's egg. As they grow, the tumours, encroaching on the orbits, may interfere with the line of vision and finally destroy the eyes. In severe cases there is a general diffuse hyperostosis of the anterior part of the maxilla. There is no pain in the tumours themselves. The superjacent skin is healthy and freely movable. The tumours are oval, with the long axes directed downwards and slightly from within outwards (Fig. 96). The nostrils are bulged inwards and more or less obstructed. The hard palate is often affected, resulting in the most hideous deformity. General glandular enlargement may be noted. Trauma seems to predispose to the development of goundou.

A case of goundou associated with tertiary syphilis was described in London by Sharpe. The patient had never been in the tropics. The lesions resembled the paranasal swellings so characteristic of goundou.

According to recent accounts, cases of goundou in Jamaicans invariably give a positive Wassermann reaction.

The bony outgrowths, not necessarily bilateral, are attached to the nasal bone and nasal process of the maxilla, but, according to Botreau-Roussel and Clapier, they are not entirely confined to this region ; a similar hyperostosis may co-exist on the tibia, upper or lower jaw, forearm, femur, or clavicle. There is a general opinion at present that goundou is a systematized hypertrophic osteitis connected in some way with yaws.

The bony changes of goundou consist of hyperostosis, which may be limited to the ascending or nasal processes of the superior maxilla, or be more widespread and affect the other bones of the skull as well, with an ever-present tendency to the formation of bosses of overgrowth and to the obliteration of adjacent cavities. The underlying pathological process is an osteo-periosteal dyscrasia, and the end-result is the production of finely-porous bone.

As yaws and syphilis are so closely allied, it might be expected that similar lesions might be found in the generalized osteitis of syphilis, but there appears to be very little evidence of it. There is very little difference between the bony changes of goundou and those which have been called *leontiasis ossea*, and, according to Stannus, hyperostosis of the facial bones has also been recorded in Paget's disease—*osteitis deformans*. According to modern knowledge, it seems possible that goundou is more akin to *osteitis fibrosa*, due to interference with the bony metabolism and an endocrine disorder, and it may well be that in this instance yaws constitutes the non-specific factor acting on an ill-fed native child

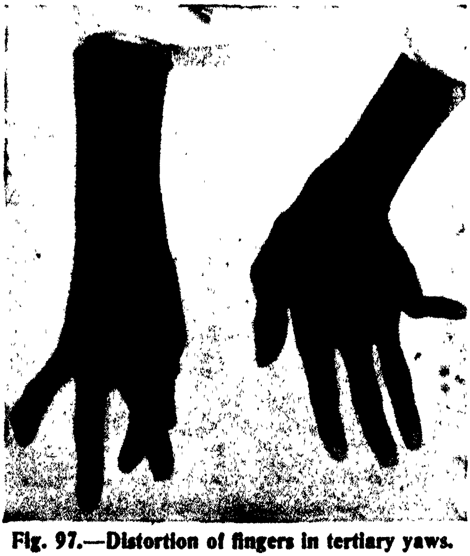


Fig. 97.—Distortion of fingers in tertiary yaws.

population. Goundou-like swellings in horses, monkeys and young pigs ("cachexie osseuse") point to osteitis fibrosa as the initial stage of this condition and all changes between cystic disease of the bones and hypertrophic exostosis can be traced in a series of skulls.

Treatment consists in incising and displacing the periosteum and chipping away the bony outgrowth with a chisel. Early cases, according to Botreau-Roussel, yield to intravenous and intramuscular injections of neosalvarsan, four or more injections being necessary before improvement is observed. This observer operated with success upon 118 out of 130 cases observed on the French Ivory Coast and the reader is referred to his monograph (Masson et Cie., 1925) for further information.

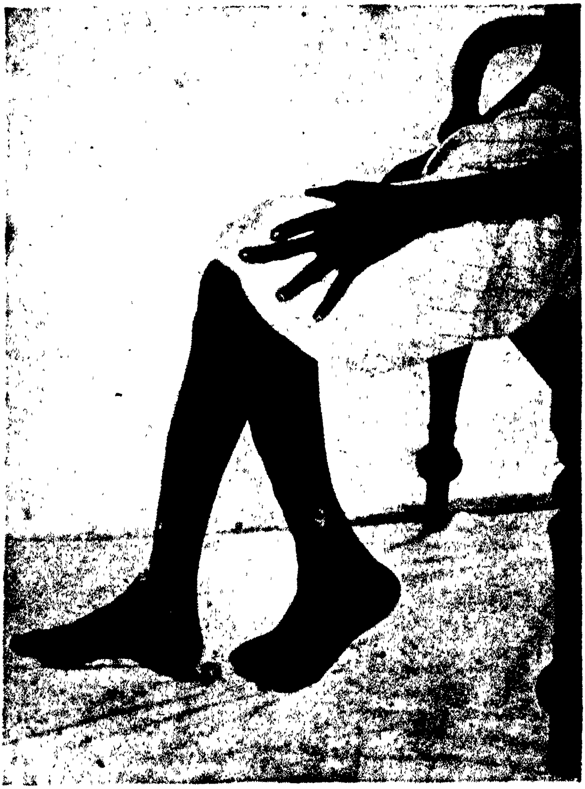


Fig. 98.—Tibial periosteal nodes, ulcers, and deformity of phalanges in yaws.

Periositis, osteitis and epiphysitis (Figs. 97, 98, 99).—Circumscribed painful periosteal nodes are frequently found on the anterior aspect of the long bones, especially the radius, ulna, and tibia. The swellings are hot and exquisitely tender, and the superjacent skin is tense and stretched. After the subsidence of the acute stage, hard, firm periosteal nodes remain. A diffuse osteitis may result in a sabre-shaped deformity of the long bones, especially the tibia and occasionally the arms and fingers. A rarefying process is also at work, for such bones are subject to spontaneous fracture with resulting malunion, accidents which are common in districts in which yaws is endemic. Hackett, who has studied the sabre-shaped tibiæ of the aborigines of Australia, believes that syphilis does not occur among these peoples, and that the bone lesions are due to yaws. Colloquially known as " boomerang leg," the deformity is an antero-posterior curvature below the knee with a forward convexity; occasionally there are bosses of localized periostitis. Radiographs show that areas of rarefaction appear early, and the bone becomes deformed. The appearances depend upon the severity of the initial lesion and the time which has elapsed since the onset of the disease. Other lesion of yaws, including gangosa, have been noted in Central and Northern Australia. A chronic periostitis of the clavicle is frequent in Fiji. These bone changes are accompanied by intense rheumatic pains, and have received distinctive names, such as " sasala."

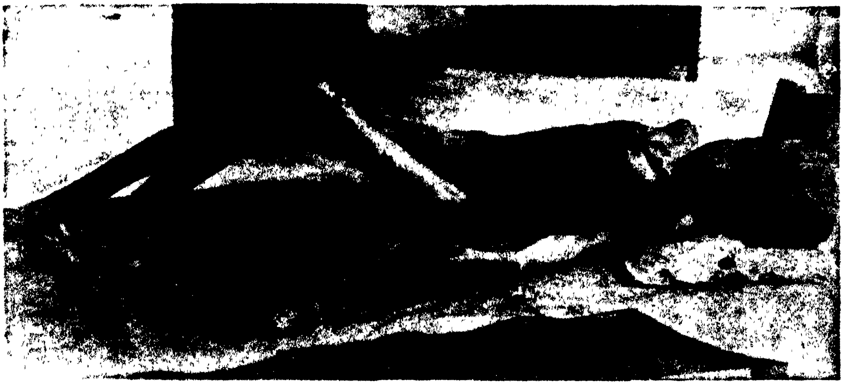


Fig. 99.—Sabre-like deformity of tibia, radius, and ulna, and multiple cutaneous ulcerations in yaws.

Juxta-articular nodules.—Fibrotic tumours situated over the olecranon, the lower end of the femur, and in other situations on the long bones, are now regarded as a tertiary phenomenon of yaws. Formerly they were regarded as constituting a disease *sui generis*, but those cases which have been investigated invariably give a positive Wassermann reaction. Originating subcutaneously, these nodules may reach the size of a small orange (Fig. 100). They are remarkably painless, and very rarely ulcerate or suppurate. Juxta-articular nodules are generally multiple, and usually in the neighbourhood of the joints, but, according to Steiner, may occur scattered over the body. Similar lesions have been described in tertiary syphilis, and the *Spirochæta pallida* has been isolated from them (Hu and Frazier), while Hudson found the same nodules in " bejel," the non-venereal syphilis of the Arabs, among whom they occur in 2·1 per cent.

of the adult male population and are known locally as "rik." According to Frontoynant and Girard, they contain uric-acid crystals. In Africa they are apt to be mistaken for *Onchocerca volvulus* cysts.

Skin lesions.—Healing of subcutaneous gummata is frequently followed by depigmentation of the skin, resulting in light-coloured or leucodermic patches, especially visible in native races. A macular depigmented exanthem limited to the hands, wrists, feet and ankles is pathognomonic of yaws and was first described by Ziemann as " melung."

After effects.—Contractions resulting from scar tissue may lead to partial ankylosis of joints, in severe cases to the destruction of lymph-channels and to the production of elephantiasis in the affected limb.

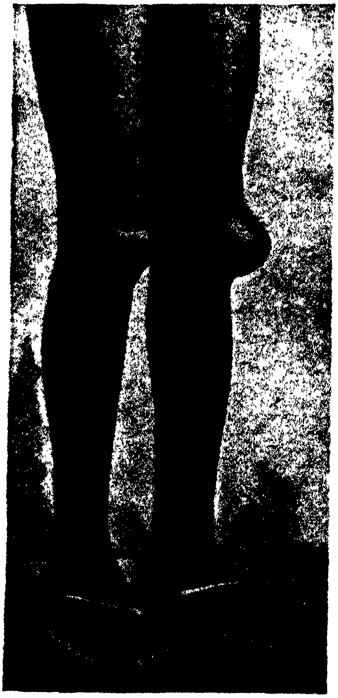


Fig. 100.—Juxta-articular nodules.
(*Photo : Dr. Watt.*)

Synovitis.—Chronic synovitis, analogous to that of tertiary syphilis often associated with bone lesions, and, it may be, with disorganization of the joint, has been recorded.

Ganglion and other lesions. — The frequency of tenosynovitis and ganglion-formation in the region of the wrist was noted by Graham, Moore, and other observers. These ganglia are usually associated with tenosynovitis and, as extra proof of their origin, they both respond in a remarkable manner to treatment with neosalvarsan and bismuth. Stricture of the mouth due to tertiary yaws has been recorded.

The general health.—Except during the initial fever, or during one of the recurring febrile relapses, the general health is not, as a rule, affected. Occasionally, however, there are debility and cachexia ; or there may be enlargement and tenderness of the lymphatic glands. In other instances rheumatic pains may be very severe.

Immunity.—After the subsidence of the secondary stage immunity is produced, but Sellards and Goodpasture demonstrated that this is relative only, for they successfully re-inoculated with the disease patients who had undergone a course of salvarsan treatment. Apparently, saturation of a community with yaws virus produces a relative immunity to syphilis. On these grounds may be explained the well-authenticated fact that syphilis is absent amongst the Polynesians of Fiji, Tonga and Samoa, in whom yaws is especially prevalent. Formerly Fijians were in the habit of inoculating their children against yaws to protect them from subsequent attacks. As far as accurate experiments have gone, immunity in syphilis is acquired much earlier than in yaws.

Duration and recurrences.—Yaws lasts for weeks or months or years, its duration depending on general health, idiosyncrasy, hygienic conditions, and the treatment. Mild cases in healthy subjects terminate in about six weeks ; though the average duration of an attack is estimated at about one year. In other instances, especially in the debilitated, the disease runs on for months, successive crops of eruption being evolved. Sometimes these recurrences may stop short at the stage of desquamation, or at the papular stage, or they may proceed to the formation of typical yaws. They are usually preceded by feverishness, pains in the bones and joints, and the successive crops may either be limited and partial in their distribution, or general.

Sequelæ.—Contrary to general opinion, Harper in Fiji believed that late manifestations of yaws occur as in syphilis and that they produced neurological conditions resembling those of locomotor ataxia and general paralysis. Lambert recorded in the South Pacific 42 Melanesians and Polynesians who died in Samoa of G.P.I. ; furthermore, aneurysmal dilatation and aortic disease were comparatively common.

Chossier, in routine post-mortems in Haiti, found aneurysms and other arterial degenerations in chronic yaws, but more recent writers (Blacklock), in assessing the clinical differentiation of yaws and syphilis, have once more remarked upon the comparative rarity of visceral and neurological lesions of the latter amongst native races. In yaws the Wassermann reaction of the cerebrospinal fluid has been generally found negative, especially in the tertiary stages. Chesterman emphasized the comparative frequency of new growths following yaws and has recorded melanoma, implanted upon crab yaws of the foot.

Mortality.—Although in the literature reference is made to deaths from yaws, yet, judging from the statistics collected by Nicholls, the mortality must be small indeed.

Diagnosis.—A painless, insensitive, larger or smaller, circular, encrusted red, granulomatous excrescence occurring in an endemic district is almost certainly yaws. The most important point about yaws, both in diagnosis and in ætiology, is its relationship to *syphilis*. Both diseases may occur in the same individual (Powell cites two cases, and Charlouis two, of syphilis supervening on yaws) ; and antecedent syphilis certainly does not confer absolute immunity to yaws, nor antecedent yaws to syphilis. The serum in both diseases gives a positive Wassermann reaction. Yaws may die out in a community, as in British Guiana (Daniels), yet syphilis remain ; yaws may be universal in a community, as in the Fijians, Tongans and Samoans, and yet true syphilis, whether as an acquired or as a congenital disease, be unknown. In yaws, Hutchinson's famous syphilitic triad—the characteristic notched teeth, nerve deafness, and interstitial keratitis—are absent.

Table IX shows the main points of differentiation.

TABLE IX

YAWS	SYPHILIS
Not congenital.	Congenital.
Primary sore—extragenital.	*Primary sore*—usually genital.
Secondary stage	*Secondary stage*
(*a*) Typical yaw pathognomonic; furfuraceous desquamation and plantar lesions characteristic.	(*a*) Seldom imitates frambœsia.
(*b*) Mucous membranes not affected.	(*b*) Mucous membranes affected.
(*c*) Itching common.	(*c*) Itching rare.
(*d*) Alopecia unknown.	(*d*) Alopecia may occur.
(*e*) Eyes unaffected.	(*e*) Iritis common; choroiditis and retinitis rare.
Tertiary stage	*Tertiary stage*
(*a*) Visceral lesions absent.	(*a*) Visceral lesions occur, e.g., pericellular cirrhosis, gumma of liver, kidney.
(*b*) Nervous system not usually affected.	(*b*) Nervous system liable to infection: tabes, G.P.I.
(*c*) C.S. fluid always negative Wassermann (Fischer; Turner, Saunders and Johnson).	(*c*) C.S. fluid usually positive Wassermann.
(*d*) Blood-vessels: no endothelial proliferation as in syphilis.	(*d*) Endarteritis obliterans of viscera —cerebral thrombosis.
Yaws better resisted. Constitutional disturbance slight; great exuberance of eruption and cheloid scarring.	Syphilis attacks constitution, affecting the vital structures.
Does not respond to mercury.	Responds well to mercury.

Secondary yaws may have to be differentiated from bromide rashes.

TREATMENT

General measures.—All are agreed on the propriety of endeavouring, by good food, tonics and occasional aperients, to improve the general health. Most are agreed on the propriety of endeavouring to procure a copious eruption by stimulating the functions of the skin—by warm demulcent drinks; by a daily warm bath with plenty of soap; and, during the outcoming of the eruption, by such diaphoretics as liquor ammoniæ acetatis and guaiacum. Warm clothing is indicated. In crab yaws a local application of 2 per cent. tartar-emetic ointment in vaseline is very useful.

I. Salvarsan, neosalvarsan (Neoarsphenamine[1]).—Except where much bone destruction has taken place, salvarsan, or better still its more recent and more soluble derivatives, has an almost magical curative effect upon yaws in every stage of the disease. The most generally used drug at the present time is neosalvarsan (neoarsphenamine). It is given intravenously to adults, and, if possible, to children; or intramuscularly (0·4 grm. dissolved in oil, into the buttock). The more urgent symptoms yield much more rapidly than do those in syphilis, and relapses are not so common. Since the introduction of salvarsan the natives of the Congo dislike being treated until the secondary rash is well out. For adults the intravenous dose advocated is 0·6–0·9 grm.; for young adults 0·6 grm., for children up to ten years of age 0·3 grm., and for children under two years, 0·1 grm.

---

[1] Throughout this account the terms arsphenamine and neoarsphenamine are given as t

The systematic use of neosalvarsan in a yaws community would, if thoroughly carried out, promptly get rid of the endemic disease, and, wherever possible, it should be enforced. The average time to effect a clinical cure is eleven days. In Samoa it has been found necessary to give three injections of 0·6 grm. of neosalvarsan, at weekly intervals, for an adult male, and appropriately smaller doses for women and children. Babies are treated by intramuscular injections. Moss in San Domingo found that the cure after three injections is permanent. The great objection to mass treatment of native populations with the salvarsan compounds is their prohibitive cost. Apparently, mercury and potassium iodide have little therapeutic action in yaws of adults as compared with syphilis, but in breast-fed children these drugs will cure the infant through the mother's milk.

II. Bismuth.—The successful treatment of syphilis by Fournier with sodium-potassium-bismuth tartrate led to the adoption of a similar method in yaws. The considered opinion of workers is that none of the many bismuth preparations can be said to take the place of the synthetic arsenicals in African yaws and syphilis. The most active form appears to be the *sodium tetra-bismuth tartrate* in both secondary and tertiary yaws.

All preparations act more efficaciously when given in the early stages. Injections should be made deep into the subcutaneous fascia, and occasionally some induration and abscess-formation may result. When treating natives on a large scale, a soluble form of sodium-bismuth tartrate (*Sobita*[1]), is preferable. This was introduced by J. O. Shircore, and is now manufactured locally in East Africa. The dose is 3 gr. dissolved in 3 c.c. of distilled water, or in oil injected intramuscularly; for children up to two years, ½–1 gr; from two to eighteen years, 1–2 gr.; and for aged persons 1½–2 gr. The generally accepted dosage for an adult is 1½–4 gr. weekly with a total dosage of 6–14 gr. Children tolerate relatively larger doses than adults. Since 1924, over a million cases have been treated in Tanganyika alone by this method.

Rutter adopted sobita as the standard method of treatment in the Solomon Islands. Three consecutive injections resulted in the healing of 66 per cent. of secondary and 78 per cent. of late tertiary lesions, but relapses tended to occur within six months, though this tendency is less in the late tertiary than in the secondary stage. No significant differences could be observed between neosalvarsan and sobita during this investigation.

In patients with septic mouths, stomatitis and albuminuria are apt to ensue as a result of this bismuth treatment. Other toxic effects are diarrhœa and skin rashes, while lassitude and articular pain occur in some cases. This, and the fact that three or more injections are necessary, have been the greatest objections to the general use of bismuth, especially in the Solomon Islands and the Congo. On the whole, the toxic effects of bismuth are less frequent and are milder than those of mercury and salvarsan. In Jamaica, the dioxide of bismuth is preferred, and next in favour is the oxychloride. Bismuth salicylate is also used in 10 per cent. suspension in olive oil. In Jamaica six to ten treatments are given. In the waging of a great anti-yaws campaign, as at present in Kenya and Tanganyika Territory, bismuth has the undoubted advantage of cheapness, costing less than half a farthing a dose. According to Hanschell, stomatitis may be avoided if injection is made into the deep subcutaneous tissues, rather than intramuscularly, and the resulting pain may be mitigated.

---

[1] This preparation is placed on the market by Howard & Sons.

Bismostab (Boots) is metallic bismuth suspended in glucose solution. When given deep-subcutaneously, it is practically painless. The dosage is 20 cg. (3 gr.) locally, and a total of 6 grm. (90 gr.) can be given altogether in refractory cases. In the tropics, however, preparations of bismuth metal have been abandoned as they are apt to block the needles.

Casbis (Bayer), a sterile oily suspension of bismuth hydrate in fine dispersion, is highly spoken of on account of the fineness of the suspension. Adults receive 0·5–1 c.c. doses, and the total dosage is 12–15 c.c.

III. Combined treatment.—According to latest reports, the combined *neo-bismuth* treatment is the most effective. By combining bismuth and neosalvarsan (neoarsphenamine), in alternating weekly injections, the chances of severe reactions are reduced. Neosalvarsan is given intravenously and bismuth intramuscularly. Attempts to combine the two preparations in one compound are now being made. *Bismuth arsanilate* (Martindale) in sterules containing Bi_2O_3, 53 per cent., arsenic, 17 per cent., given by injection, has been tried in Tanganyika and Nigeria. Other preparations, known as *neotreparsenan* and *bismuth arsphenamine sulphonate*, are given in doses of 20 cg. (3 gr.) per week up to a total of 6 grm. (90 gr.). It is said that the addition of 0·1 c.c. of *butyn* exerts a local anæsthetic effect. A French preparation, which is well tolerated, is known as *Bivatol.*

IV. Arsenical preparations given by the mouth.—*Stovarsol* is a much more convenient method of mass-treatment than injections of salvarsan. It is customary to commence with 1 grm. daily, increasing to 1½, 2, and 3 grm. on successive days for adults; ½–1 grm. for children. After a total of 8–15 grm., according to van den Branden and Lefrou, the Wassermann reaction becomes negative. Chesterman considered three courses necessary to effect a cure, but found that he could give in stovarsol ten times the corresponding dose of neosalvarsan. Slight diarrhœa is the only untoward symptom of intolerance occasionally observed, though he gave as much as 2 grm. to children at a single dose. One objection to stovarsol is that the full course may be more expensive than injections of salvarsan. *Halarsol* (May & Baker), oxyamino-phenyl-dichlorasine, in intravenous and intra-muscular injections in doses of 0·125 to 0·25 grm. for three doses at three- to four-day intervals, has been proved on the Congo to be efficacious in all stages of yaws. The minimal toxic dose is 4·5 mgm. per kilo.

Carbarsone, p-carbamino-phenyl arsonic acid, first prepared by Ehrlich, contains 28·85 per cent. of arsenic. It is given in the same doses as stovarsol and the therapeutic dose is 75 mgm. per kilo bodyweight. A number of other preparations for the treatment of yaws and tropical syphilis are detailed in Chap. 49, p. 828.

Prophylaxis resolves itself into the adoption of measures to prevent contagion. These are the isolation and segregation of the affected ; the dressing and treatment of wounds in the hitherto unaffected ; the application of antiseptic ointments to yaws sores, so as to obviate the diffusion of spirochætes by flies ; the purifying or destruction by fire of houses or huts notoriously infected ; the prevention of pollution of bathing-water by yaws discharges ; and, especially, the prompt treatment of the infected by salvarsan and bismuth.

CHAPTER XXXIII

MYCETOMA AND BLASTOMYCOSIS

Synonyms. Madura Foot ; Pseudactinomycosis.

Definition.—A fungous disease of warm climates, affecting principally the foot, occasionally the hand, rarely the internal organs or other parts of the body. It is characterized by enlargement and deformity of the part ; an oily degeneration and general fusion of the affected tissues. The disease runs a slow course, is never recovered from spontaneously, and, unless removed, terminates after many years in death from exhaustion.

History and geographical distribution.—It was first described by Kämpfer in 1712. Subsequently it was confused with tuberculous disease. Carter, from 1865 to 1874, furnished the information upon which modern descriptions are based, and since then further advances have been made by Bouffard and Brumpt.

In India, mycetoma is endemic in widely scattered districts, although whole provinces, as that of Lower Bengal, enjoy an almost complete immunity. It appears to be acquired only in rural districts, the inhabitants of the towns being exempt. Among the more afflicted districts may be mentioned Madura—hence the name " Madura foot " by which mycetoma is often known—Delhi, various places in the Punjab, Kashmir and Rajputana. In recent years we have had accounts of its occurrence with some degree of frequency in Senegambia, Somaliland, Aden, Algeria, Egypt, the Sudan, Madagascar, Cochin-China, Italy, the United States, and South America. The following varieties have been described :—

i. ACTINOMYCOTIC MYCETOMA

Caused by the ray-fungus, *Discomyces bovis* (Harz, 1877). Actinomycosis has a world-wide distribution and is a common disease of cattle. It destroys bone by erosion and spares only nerves and tendons. The pus from the affected region contains small yellowish granules (" sulphur grains ") of irregular shape, attaining at most 0·75 mm. in diameter. They are soft and consist of an inextricable felted mass of mycelium. The threads are radially arranged at the periphery of the grain, and their free extremity widens into a bulbous, club-like termination (10–20 μ long by 8–10 μ wide). These clubbed ends have been looked upon by several authors as forms of degeneration.

ii. VINCENT'S WHITE MYCETOMA

Caused by *Discomyces maduræ* (Vincent, 1894). This kind of mycetoma is common and widely distributed. It has been observed in Algeria, in Abyssinia, in Somaliland, in Cyprus, in India, in Argentina, and in Cuba.

Unlike *D. bovis* and other mycetoma-producing fungi, it does not destroy bone, and does not seem to act directly on the general health of the patient, though ultimately and indirectly it may bring about cachexia.

iii. NICOLLE'S WHITE MYCETOMA

Caused by *Sterigmatocystis* (*Aspergillus*) *nidulans* (Eidam, 1883). So far, only a few cases have been observed, by Nicolle and Pinoy, in Tunis, but probably it occurs in many places, the parasite *S. nidulans* being widely distributed.

Primary infection probably takes place from barley grain. The grains formed by this fungus may also attain the size of a pea, but they differ from those of *Discomyces maduræ*, inasmuch as they are more or less spherical and present a smooth surface.

iv. BOUFFARD'S BLACK MYCETOMA

Caused by *Aspergillus bouffardi* (Brumpt, 1906). The grains are quite characteristic. They are black and vary in size from a pin's head to that of No. 1 shot. They present a mulberry-like surface which is smooth and glossy, the structure consisting of a coiled-up mass.

v. CARTER'S BLACK MYCETOMA

Caused by *Madurella mycetomi* (Laveran, 1902): This mycetoma has a very wide distribution. It has been observed in Italy, in Africa (Senegal, French Sudan), and in India.

The grain formed by *Madurella mycetomi* is dark-brown or black. It measures 1 to 2 mm. in diameter, is hard and brittle ; its surface is irregular and frequently presents pointed eminences which differentiate it from the larger and smooth grains of *Aspergillus bouffardi*. The grain is composed of white threads, always over 1 μ in diameter and attaining at times 8 to 10 μ, which secrete a dark-brown substance that cements them together.

vi. BRUMPT'S WHITE MYCETOMA

Caused by *Indiella mansoni* (Brumpt, 1906). This form was described from a specimen of Indian origin in the museum of the London School of Hygiene and Tropical Medicine.

The grains peculiar to this form are hard, white, and very small, varying in size between ⅛ and ¼ mm., and having a lenticular shape. Some are bean-shaped and flat. To study their structure it is necessary to boil them first in a solution of caustic potash. The hyphal threads are large and closely set, but without any cementing substance between them. The periphery of the grain contains numerous large chlamydospores having thick walls and being full of protoplasm.

vii. REYNIER'S WHITE MYCETOMA

Caused by *Indiella reynieri* (Brumpt, 1906), originally described by Reynier from a specimen in Paris ; a second case has been recorded from Greece.

The grains may attain 1 mm. in diameter ; they are soft, white, and consist of a coiled-up strand which gives them a peculiar appearance resembling the excrement of earthworms.

viii. BOUFFARD'S WHITE MYCETOMA

Caused by *Indiella somaliensis* (Brumpt, 1906). This form is perhaps even more common in India than Vincent's white mycetoma. Bouffard has found it twice in Somaliland.

Indiella somaliensis is a most destructive fungus. In a foot examined by Brumpt all the muscles, tendons, and bones had been replaced by sclerosed tissues, more or less homogeneous, presenting numerous sinuses full of yellowish grains clustered together like fish-roe, and many small inflammatory nodules containing one or more grains.

Culture.—Cultures can be made, as in actinomycosis, both under äerobic and anäerobic conditions on glucose or glycerol-agar plates, in shake cultures or in Loeffler's serum. Some workers recommend keeping cultures in an atmosphere of CO_2. The medium should be inoculated directly with colonies from the pus but, owing to slow growth of the actimonyces, pure cultures are somewhat difficult to obtain, unless the pus is free from contamination with other organisms.

Pathology.—On cutting into a mycetomatous foot or hand the knife passes readily through the mass, exposing a section with an oily, greasy surface, in which the anatomical elements in many places are unrecognizable, being, as it were, fused together, forming a pale, greyish-yellow mass. The bones have in parts entirely disappeared; where their remains can still be made out, the cancellated structure is very friable, thinned, opened out, and infiltrated with oléaginous material. Of all the structures, the tendons and fasciæ seem to be the most resistant.

The most remarkable feature revealed by section is a network of sinuses and communicating cyst-like cavities of various dimensions, from a mere speck to a cavity an inch or more in diameter. Sinuses and cysts are occupied by a material unlike anything else in human morbid anatomy. In the black varieties this material consists of a black or dark-brown, firm, friable substance which, in many places, stuffs the sinuses and cysts; manifestly it is from this that the black particles in the discharge are derived. In the white varieties the sinuses and cysts are also more or less stuffed with a white or yellowish roe-like substance, evidently an aggregation of particles identical with those escaping in the corresponding discharge. In the very rare red variety the colour of the accretions is red or pink.

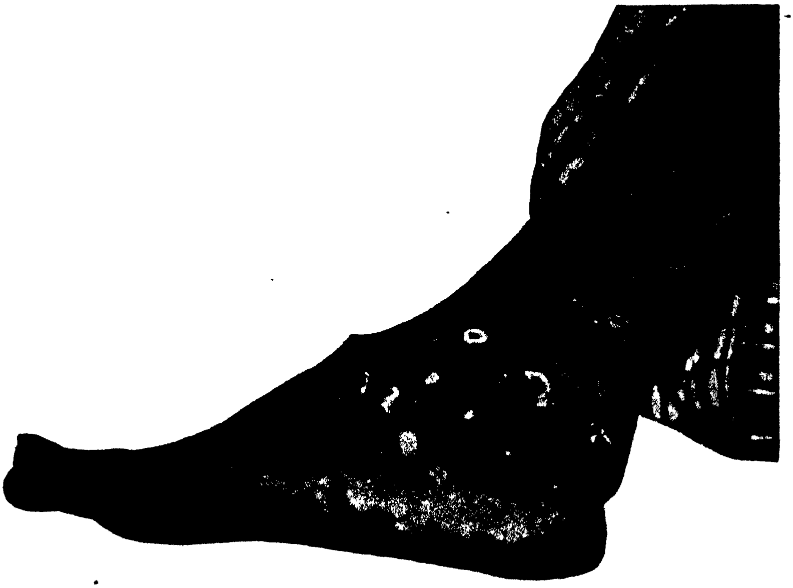


Fig. 101.—Mycetoma of about two years' standing. (*After Legrain.*)

Under the microscope the mycotic elements can be readily recognized in the concretions. In microscopic sections of the tissues, evidences of extensive degenerative changes, the result of a chronic inflammatory process, can be made out. An important feature is a sort of arteritis obliterans, or extensive proliferation of the endothelium of the arteries, and, according to Vincent, a thickenin of the adventitia of the vessels as well as of the capillaries in the more afl

Symptoms.—Mycetoma begins usually, though by no means invariably, on the sole of the foot. The first indication is the slow formation of a small firm, rounded, somewhat hemispherical, slightly discoloured, painless swelling, perhaps about ½ in. in diameter. After a month or rather more, this swelling may soften and rupture, discharging a peculiar viscid, syrupy-looking, oily, slightly purulent, sometimes blood-streaked fluid holding in suspension certain minute, rounded, greyish or yellowish particles, often compared to grains of fish-roe. In other examples of the disease the particles in the discharge are black, having the size and appearance of grains of coarse gunpowder. Sometimes these particles are aggregated into larger masses up to the size of a pea. In time, additional swellings, some of which break down and form similar sinuses, appear in the neighbourhood of the first, or elsewhere about the foot (Fig. 101). The sinuses are mostly permanent, healing up only in a very few instances. Gradually, the bulk of the foot increases to perhaps two or three times its normal volume (Fig. 102). There is comparatively little lengthening, but there is a general increase in thickness, so that in time the mass comes to assume an ovoid form, the sole becoming convex, the sides rounded, and the anatomical points obliterated. The toes may be forced apart, bent upwards at the tarso-phalangeal joints, or otherwise misdirected, so that when the foot is placed on the ground the toes do not touch it. The surface of the skin is roughened by a number of larger or smaller, firmer or softer hemispherical elevations, in some of which the orifices of the numerous sinuses open.

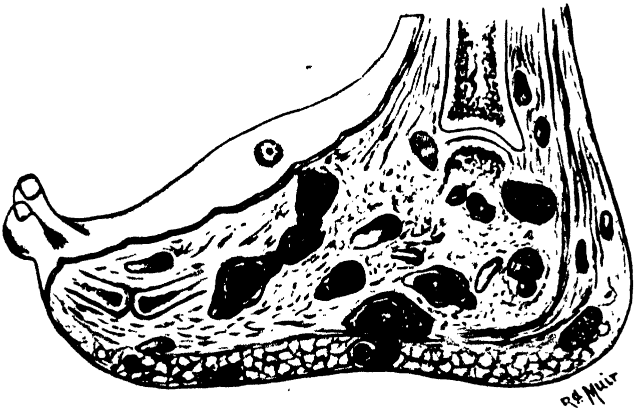


Fig. 102.—Section of a Madura foot. (*T. R. Lewis.*)

The discharge from the sinuses differs in amount in different cases, and from time to time in the same case; whether profuse or scanty, it always exhibits the same oily, mucoid, slightly purulent appearance, and may stink abominably. With a very few exceptions it contains either the grey or the black grains, rarely reddish or pink ones.

As the foot enlarges, the leg atrophies from disuse; so that in the advanced disease an enormously enlarged and mis-shapen foot, flexed or extended, is attached to an attenuated leg consisting of little more than skin and bone. In some cases the tibia or bones of the forearm are involved:

in others the disease at first may be confined to a toe, or a finger, or other limited area. In a very few instances the seat of the disease is the knee, thigh, jaw, or neck. Unless the case be one of actinomycosis, the internal organs are never implicated, either primarily or secondarily. The lymphatic glands, likewise, although they may show adenitis from secondary septic infection, are very rarely involved.

After ten or twenty years the patient dies, worn out by the continued drain, or carried off more suddenly by diarrhœa or other intercurrent disease.

Treatment.—The only effective treatment is amputation, well above the seat of the disease ; for the long bones may be implicated, as well as the small bones, and unless the entire disease be removed, it will recur in the stump. Complete removal is not followed by relapse. If a toe, or a small portion of the foot or hand, is alone involved, this may be excised. Potassium iodide in large doses has been found beneficial in certain forms.

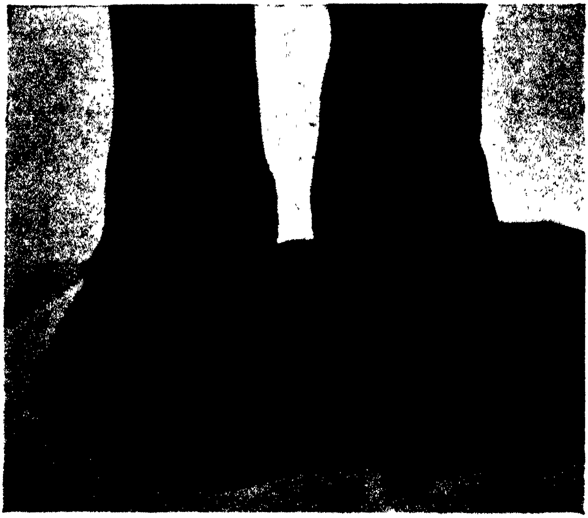


Fig. 163.—Chromoblastomycosis of feet, "Mossy foot," from British Guiana. (*Dr. Wase-Bailey.*)

Buchanan recommended surgical removal of as much diseased tissue as can be conveniently reached. Then tincture of iodine should be injected into any suspicious area remaining, in the hope that the surviving elements will be killed ; therefore 1–2 c.c. of iodine should be injected every ten days for at least two months. At first, the local reaction is not severe, but later it becomes so. Probably a less irritating solution, such as Lugol's, would be better.

Potassium iodide should be given by the month in large doses over a considerable period, and there are those who think that the French tincture of iodine is more effective if administered in frequent doses of 2 drops in milk. Quite recently, the sulphonamides—sulphapyridine and sulphathiazole—in full doses have been found effective in actinomycosis of the bowel, and therefore should be given a therapeutic trial in Madura foot.

BLASTOMYCOSIS

This term is used to indicate lesions, other than mycetoma, produced by the proliferation of certain yeast-like fungi in the tissues. Normally these are either saprophytic or live as parasites on animals or plants, and appear to be especially abundant in tropical countries. Doubtless they get access to the human tissues through some wound or breach of surface. The following clinical types have been recognized:

I. Chromoblastomycosis "Mossy foot" (Fig. 103).—A papillomatous condition of the legs and feet first described by W. Thomas in the Amazon Valley, Brazil, but now reported from Honduras, North, East and South Africa, Porto Rico, Southern United States, Dutch East Indies, Japan, South Russia and Rhodesia.

The disease is due to an infection of the skin with a fungus—*Phialophora verrucosa* (Thaxter, 1915). The organism has also been named *Fonsecæa compactum* or *F. pedrosi*. The fungus can be cultured on ordinary media, and forms a blackish growth in stab cultures on ascitic agar or serum media. Chlamydospores 8–15 μ in diameter, as well as conidia, are produced and sometimes aërial hyphæ. The organisms are akin to the saprophytic moulds common on vegetation.

The foot and ankles—usually of males engaged in agriculture—are covered with warty outgrowths resembling barnacles, which are vascular and sometimes painful. They are usually papillomatous, but occasionally pedunculated. The sole of the foot usually escapes. It is claimed that the disease can be inoculated into the nose of rabbits producing a verrucoid mass.

The diagnosis is established by demonstration in sections of a tuberculoid type of reaction with rounded brown bodies resembling yeast cells (Simpson, Harington and Barnetson, 1943). The best treatment is actual cautery.

II. Coccidioidomycosis.—Cutaneous patches, of various dimensions, of small warty excrescences with minute abscesses or encrusted ulcers, especially at the periphery of the patch.

Coccidioidal granuloma, or Posada's Disease (Rexford and Gilchrist, 1894) was first discovered in Buenos Aires by Wernicke in 1892. It has been found especially in Brazilians, in whom it causes extensive ulceration. The pus from the lesions is easily inoculated into animals, especially guinea-pigs, in which it causes a virulent infection. Up to 1935, 400 cases had been reported, usually in Upper California, and it has also been seen in oxen, but in them produces no symptoms. It has also been found in rodents, dogs and sheep, in Arizona, Texas, Old and New Mexico. Infection is probably caused by inhalation of the spores, and the skin lesions originate round the site of scratches and other lesions.

Another form, "valley fever" or "desert fever" of the San Joaquin Valley, resembling erythema nodosum with pulmonary involvement and easmophilia, is probably a generalized infection from inhalation of chlamydospores. The affected skin patches may remain pigmented. The disease usually presents an influenza-like initial phase. Arthritis and phlyctenular conjunctivitis have been noted. Sensitivity is established within fourteen days and an intradermal test with "coccidioidin" is now employed. An epidemic in San Benito County has been reported by Davis and Smith, and it has been shown that 80 per cent. of persons who have lived in the S. Joaquin Valley for over ten years are sensitive, and also Indian children in the reservation.

The organism is *Coccidioides immitis*. The cells occur either isolated or in giant cells. They are spherical and thick-walled, with a diameter of 2–80 μ. The organism reproduces by endospore formation; budding is absent. The wall of the ascus often shows radiate formation. On all the usual media the colonies are flat and greyish, becoming white to light cream, with aërial hyphæ, which in microscopical appearance are septate, branching, hyphal swellings; arthrospores measure 2·5–7 μ in diameter; chlamydospores are abundant, 5–8 μ in diameter. Studies in metabolism of *C. immitis* show that the organism is resistant to desiccation, but the chlamydospore develops under conditions of drying, and it is impossible to infect animals in the absence of this spore. This resistance to drying is an important factor in dissemination of the organism in California. *C. immitis* has been isolated from the desert soil by Stewart, Meyer, Emmons and Ashburn. Pochet mice (gophers) and kangaroo rats form a natural reservoir of the disease.

The cutaneous type of blastomycosis also includes the following conditions:

North American Blastomycosis or Gilchrist's Disease (1894) (*Zymonema dermatitidis*).—An infectious granuloma, acute or chronic, with cutaneous or systemic lesions—papulo-ulcerative, verrucous, or papillomatous, or gummatous, showing typical violet colour. The organism has simple or budding yeast-like cells, thick-walled, 5–20 μ in diameter; the colonies on culture are yeast-like. Hyphæ are septate and branching, 2–4 μ in diameter; conidia are pyriform or round, 5 μ in diameter.

European Blastomycosis (*Cryptococcus hominis*) is clinically similar to Gilchrist's disease, but ulceration is common in the cutaneous form, with abscesses, and it quite commonly invades the cerebro-spinal system. The organism has thick-walled, heavily-encapsuled, simple or budding cells, 5–10 μ in diameter. Colonies on culture are "yeasty," smooth, mucoid or moist, and spherical or ovoid with budding encapsulated cells approximately 2–6 μ in diameter.

South American Blastomycosis, or Splendore de Almeida Disease (Lutz, 1908) (*Paracoccidioides brasiliensis*), is generalized or localized, cutaneous or systemic, the lesions being granulomatous, papular, verrucous or ulcerative. It spreads by the lymphatics. The cells are spherical or ovoid, 1–30 μ in diameter, rarely larger, with thick walls.

III. Lingua nigra.—A form occurs on the tongue, leading to hypertrophy of the filiform papillæ, and causing a condition known as *lingua nigra*. The organism is known as the *Cryptococcus linguæpilosæ*; it has a double contour, is composed of oval yeast-like cells and mycelia elements, and can be cultivated on maltose-agar. Wilkinson (1940) and others claim that *lingua nigra* can be cured by nicotinic acid.

IV. Pulmonary Blastomycosis.—*Cryptococcus capsulatus*, allied to *C. farciminosus* of the horse, has been demonstrated in the epithelial cells of the lung by Darling, who named it *Histoplasma capsulatum*. The disease it produces in many respects resembles kala-azar, and is accompanied by splenomegaly, anæmia, irregular pyrexia, and leucopenia (*see* p. 853).

Niño in Argentina has described, as *Cryptococcus pyschrophylicus*, an organism which caused a generalized infection originating from an ulcerated condition of the face. The organism grew best at 22–25° C., but was arrested at 37° C. Guinea-pigs, white mice, and rats were susceptible to inoculation.

V. Sporotrichosis.—This has been reported from Southern France, Southern U.S.A., South America, and South Africa, where it is common amongst the miners of Witwatersrand. It produces gumma-like swellings in limbs or trunk, which enlarge and ultimately break down, leaving deep ulcers, due to organisms, *Sporotrichum* (*Rhinocladium*) *beurmanni*, or *S. schenckii*, which usually exist saprophytically, and gain entrance to the body through an abrasion of the skin or œsophagus. Occasionally they may be demonstrated in the blood; the lymphatics, eye, oral cavity, periosteum, muscles, or viscera may become involved. In the discharges and tissues the parasites are scanty, so that the mycotic nature of the disease can only be made out from cultures. Benham and Kesten isolated the organism from linear nodules in the arm, and reproduced the lymphatic type of infection in a monkey. Inoculation of white rats produced typical orchitis. In man infection may be caused by a thorn prick or other injury.

Pijper and Pullinger (1927) recorded 14 cases in native miners on the South African Rand. They distinguished a primary sore in the form of a localized ulceration on a finger, or the shin. Ten of the fourteen cases had the lesions confined to one arm; the others were on the shin, with lesions extending up as high as the buttock. Incision of the nodules in the paths of the lymphatics produced pus or serous fluid.

Sporotrichum beurmanni can be isolated from the tissues by aspiration and insemination on to Sabouraud's medium. The parasite occurs in wild rats in Argentina and Brazil, while a similar disease, apt to be mistaken for epizoötic lymphangitis, occurs in horses and mules in Madagascar (Carougeau).

It appears to be a common parasite in nature, and recently (1933) Benham and Kesten have transmitted the human parasite to carnations, in which it produces a "bud rot" similar to that caused by a natural parasite, *S. poæ*.

The parasitic elements are very scanty in the pus, and in mycelial elements are seen either in sections or in cultures. Individual cigar-shaped yeast-like parasitic elements are often found engulfed by phagocytes.

Hemisporosis (*Hemispora stellata*) is a disease like sporotrichosis reported from Italy, and is characterized by granulomatous growths resembling syphilis or tuberculosis. Occasionally bones are affected.

VI. Torulosis.—This gives rise to grave lesions of the pulmonary and nervous systems, and local tumours of a peculiar consistency containing round cells surrounded by a gelatinous substance secreted by the organism. It is found especially in California. The parasite, which has been especially studied by Kessel, is known as *Torulopsis histolytica* (Stoddard and Cutler, 1916), synonym, *Cryptococcus histolyticus*. The yeast-like cells are usually found in the cerebro-spinal fluid. Experimental infections are easily produced in rats and mice by intraperitoneal injection, generalized lesions being found in lungs, liver, spleen, kidneys and brain. Kessel and Holtzwart found 45 cases reported; most have involved the central nervous system and four have exhibited general infection. In four other cases infection was localized to the muscles of the vertebral column, to pelvic and inguinal abscesses, or to the tongue or nasopharynx. In one case from Los Angeles lesions were confined to the knee. This disease appears to be incurable. The diagnosis is usually made by cerebrospinal puncture. The protein content and globulins are raised, as in other forms of meningitis; the sugar content is lowered and chlorides reduced.

T. histolytica is a primitive form of yeast cell; it multiplies by gemmation, does not produce endospores or mycelium, and can be cultured in glucose broth or on Sabouraud's medium. The colonies are glistening white, and show no mycelia penetrating into the substratum, as is characteristic of Monilia. The individual cells multiply by gemmation, no hyphæ being observed. The cells exhibit characteristic capsules. No asci are formed.

The sugar reactions are typical: no acid or gas is produced in arabinose, dextrose, galactose, inulin, maltose, mannitol, raffinose, sucrose, lactose or dextrin. The reaction in milk is alkaline. When it is inoculated intraperitoneally into rats and mice, the animals die in eight to twenty-eight days, and the organisms can be recovered from the tissues. Monkeys inoculated intracardially develop small nodules on the face, eyelids and ears, cutaneous lesions containing the organism. In some monkeys, however, a general torulosis of the brain and spinal cord develops.

Diagnosis.—Usually the lesions of blastomycosis in the first instance suggest syphilis or tuberculosis. Specific treatment and absence of reaction to tuberculin and of the tubercle bacillus should lead to a careful search for yeast-like organisms in the discharges or scrapings. Widal and Abrami found that the serum of sporotrichosis will agglutinate cultures of the specific organisms; while Malvoy and Ricketts have demonstrated a complement-fixation test in blastomycosis, using an old culture as an antigen. Martin (1935), especially, employed this method in diagnosis. The antigen was a suspension in salt solution of the organisms grown at 37° C. on beef-infusion, at *p*H 7·4, on blood-agar slants. The patient's serum was inactivated at 56° C. for fifteen minutes, and the test was carried out as for the Wassermann.

Treatment.—All forms of blastomycosis are exceedingly chronic and resistant to treatment. Surgical measures are useless, but large doses of the iodide of potassium or of sodium (20–30 gr. three times a day, well diluted) are sometimes effective, and should always be tried and, if found beneficial, continued until cure is well established. In sporotrichosis the tumours can be punctured and injected with potassium iodide, 1 in 100, while treatment must be continued for some time after apparent cure. X-rays are at times a useful adjunct. *Coccidioides immitis* is said to be amenable to sulphonamide therapy.

Section V.—DISEASES OF THE CENTRAL NERVOUS SYSTEM

CHAPTER XXXIV

NEURASTHENIA IN THE TROPICS

Psychoneuroses play a considerable part in adding to the burdens of life, and are the cause of a proportion of invaliding among European officials and business men from the tropics ; more especially from West Africa. As a cause of disability, neurasthenia or anxiety psychoneurosis, or whatever term may be applied to this real and distressing condition, has superseded tropical diseases. Therefore, from the point of view of Colonial Administration, neurasthenia is of greater importance than the majority of the tropical diseases with which this book deals. There is nothing peculiar to tropical neurasthenia which differentiates it from similar anxiety neuroses in temperate climates.

When it is considered that, in the figures quoted by Squires, no less than 45 per cent. of 358 invalidings of Europeans from the tropics were for psychological reasons, there is obviously some feature in life under tropical conditions which pre-disposes towards this state. Fully developed and frank neurasthenia, as seen in its most characteristic form, is more apt to develop in a neurotically-disposed individual than in one of a complacent and unemotional mental make-up, and it is not always possible to gauge with accuracy those individuals in whom tropical neurasthenia will eventually develop. Culpin pointed out that certain persons go to the tropics as a flight from the strain of social life at home.

In an analysis of neurasthenia in West Africa Rowland Hill (1943) found that patients with long-standing conditions of nervous instability were made worse by tropical life, but in nearly all there was evidence that the neurasthenic tendency had been exaggerated by disease acquired in the tropics.

The influence of tropical infections (p. 15).—Tropical infections, especially the enervating, debilitating, and irritating recurrent relapses of malaria, are predisposing factors. The recurrent headaches and fevers encourage patients to refer sensations to the cranium, so that they complain of neurasthenic headache, lack of concentration, loss of memory (West Coast Memory), and general disinterestedness in life. Intestinal infections, such as amœbic or bacillary dysentery, may promote concentration of thought on the intestinal tract. The patient's attention becomes rivetted on his digestive system, with the result that introspective psychoneurosis develops. In this respect tropical infections do undoubtedly predispose to "tropical neurasthenia." But there are other aspects of life in the tropics which engender introspection. The heat, insect life, the proximity to natives who cause annoyance and whose ways and psychology the European cannot understand, the dull monotony, the ever-recurring twelve hours of daylight alternating with twelve hours of pitchy night, and the abundant and vexatious insect life; all act as stimuli which goad to the neurasthenic state. The dulling of the appetite engendered by heat, the unpalatable and unsuitable food, the greasy cooking, the abundance of starchy matter, the monotony of tinned foodstuffs, together with the comparative absence of essential vitamins, all tend to upset the digestive apparatus and to depress the higher psychical centres.

Fear of disease and hypochondriasis are sources of neurasthenia in previously healthy and well-balanced people who, after serving in the tropics for long periods, have suffered a good deal of illness without much deterioration, but with loss of confidence in their ability to stand tropical life. All those who have a tendency to anxiety neurosis are made worse by exposure to heat.

Sleep.—Insomnia, which appears to be the outward manifestation of physical exhaustion and which nearly always appears towards the end of the tour in tropical Africa, is usually the first manifestation of the neurasthenic state, and imperatively indicates invaliding to a temperate climate.

Sexual factors.—Other factors will occur to anyone who has lived in isolation under tropical conditions. There is the sex factor, which may be potent; there is the social isolation which operates in out-stations; in others it is excess of alcohol, late hours, or living an unaccustomed life attended by native servants—all these may upset the mental equilibrium. Then there is, too, the constant restraint and watchfulness required to avoid offending against local prejudices, and having to live with others who are also in a state of constant exasperation.

Work and exercise.—Probably hard mental and physical work, in moderation, act as a bar rather than as a predisposing factor in the development of neurasthenia. Mental occupation tends to divert the mind from self-interest. On the other hand, mental pressure or undue stress appears to be less easily tolerated in the tropics than at home. Neurasthenia is not a special affliction of Europeans, for it is frequently observed amongst the educated native officials in West Africa, Malaya and India, though the proportion is by no means so great as in Europeans.

Neurasthenia in women.—It is difficult to state the sex incidence of neurasthenics; probably women, with their more highly developed emotional centres, are more apt to develop it, granted equal opportunities, than men.

A tropical climate usually produces certain psychological effects in women. Those who become neurasthenic suffer from pelvic pain and discomfort, menorrhagia and toxæmia. Constipation, by favouring pelvic congestion and inflammation, and uterine displacements, have also to be considered.

The effect of the tropical climate on the newly-arrived European woman is at first distinctly exhilarating. The appetite is increased and the heat does not oppress her at first as it does in succeeding years, and she has a feeling of well-being. Menstruation frequently stops for a season. The sense of well-being may be so real that risks are taken which more experienced residents avoid, such as eating unsuitable food. The long hours that European women spend in shaded houses during the heat of the day engender a feeling of lethargy, due to extra work thrown on the liver, and want of exercise.

Childbirth in European women in the tropics is apt to be more difficult and laborious than in temperate climates, due very probably to the conditions of life; but even among native women between 30 and 40 per cent. of deaths are directly or indirectly connected with parturition. Native women, as a rule, give birth with extraordinary ease, and only where they have departed from a natural mode of life, and are living in seclusion, is parturition difficult.

The effect of tropical conditions.—Tropical life may have a disturbing effect on the mentality of even the most healthy and balanced individual. After a year or more of constant exposure to heat and humidity, the hours of sleep become disturbed, and the nervous system more sensitive to external stimuli. Insomnia may be precipitated by certain electrical conditions of the atmosphere, at present little understood, skin conditions, especially prickly heat, and possibly a hyperglycæmia which Dutch investigators in Java ascribe to the climate. Otherwise healthy adults often appear "nervy" and "excitable," showing exaggerated reflexes and nervous twitchings of the face and limbs, with increased reflexes, directly they return to a temperate climate. In the minor states of disturbance the fears and stresses disappear the moment cool headwinds are encountered, and peaceful and refreshing sleep is enjoyed once more. But transference to his home climate does not immediately relieve a fully-developed neurasthenic of his fears; on the contrary, the hum and bustle around him act as further stimuli.

The effect of quinine.—In certain individuals the constant absorption of prophylactic quinine has a depressing effect. It may be a direct mental depressant; on the other hand, it may act indirectly by causing indigestion and abdominal discomfort. This subject has been discussed on p. 115, and it is open to question whether more harm, in the neurasthenic sense, is not done to some people by constant quinine, than is counterbalanced by such protection as the practice affords.

Symptoms.—The very appearance of the individual betrays his mental state. He (or she) is emotional to a degree, so that any sympathetic reference to health may provoke a flood of tears. There are others in whom the most profound depression reigns, and who may display suicidal tendencies; these are usually associated with intractable insomnia.

The patient usually complains of a headache confined to the temporal or parietal portion of the cranium. There is a sense of increased intracranial pressure. Others experience a sinking feeling in the abdomen, or indefinite abdominal pain, or flatulent dyspepsia. There is usually a mild tachycardia, or rather vasomotor instability, with a fall in blood-pressure and a diastolic pressure below 80. The reflexes are usually exaggerated, and there may be a false ankle-clonus with hyperidrosis of the palms of the hands and of the feet.

It has been suggested that the main symptoms are to be ascribed to hyperthyroidism, but the Editor has been unable to find any evidence for this hypothesis. With this degree of nervous instability it is not surprising to find divergence of the pupils on accommodation (Mœbius' sign) which by some is considered to indicate hyperthyroidism.

Treatment.—The main principle in treatment is to remove the patient from his immediate surroundings to a temperate climate with congenial companions. Usually, on arriving in a cool climate, natural sleep sets in and fears and anxieties disappear. The neurasthenic state may be temporary. On the other hand, the emotional and depressive states should be treated seriously and efforts should be made to discover some underlying infection. The Editor has on several occasions seen profound neurasthenic symptoms disappear after treatment of an underlying unsuspected malaria. If alcohol has been taken in excessive amount, it must be cut down, or prohibited altogether. Efforts should be made to divert the patient's attention from himself. Hobbies of all kinds should be encouraged and there is probably no occupation more restful and curative than fishing in Scotland or Ireland.

For insomnia, mild hypnotics should be prescribed, such as allonal, luminal, or medinal. Sleep may be induced by a hot bath or a cup of Ovaltine. As a general sedative a mixture of the following type may be prescribed, to be taken three times daily:

Ammon. brom.	gr.x (0·648 grm.)
Spirit. ammon. aromat.	♏xv (0·888 c.c.)
Syrup. aurant.	ʒi (3·55 c.c.)
Aq. menth. pip. ad	℥ss (14·21 c.c.)

℥ss three times a day after meals.

Prophylaxis.—As the main treatment of neurasthenia entails removal from immediate surroundings, its prevention is difficult. Once marked neurasthenia has developed in a European in the tropics, he should be invalided to a temperate climate and his return becomes a matter for anxious consideration. There are cases in which the patient quickly regains his mental equilibrium; but should the mental depression continue, in spite of the simple methods recommended, then permanent invaliding should be considered. The Editor is of opinion that a patient with well-marked tropical neurasthenia should never be permitted to return, otherwise the old symptoms will reassert themselves directly he arrives in his old haunts, so that after a few months he will be sent home again.

CHAPTER XXXV

ENCEPHALITIS JAPONICA

Synonym. Japanese Type B encephalitis.

Encephalitis japonica is, strictly speaking, an epidemic encephalomyelitis involving the brain and spinal cord, and is to be distinguished from epidemic encephalitis (encephalitis lethargica) by the absence of eye lesions and other features to be detailed later.

Epidemiology and geographical distribution.—Encephalitis japonica, as its name implies, is well known in Japan, where it apparently has occurred in epidemic waves since 1871. In 1933 it was found in different portions of North America (St. Louis; Toledo; Kansas City; Paris, Ill.; and St. Joseph, Mo.). In 1938 it was recognized by Pette as occurring in Germany and by Silbermann in Vienna. In 1928 Kaneko and Aoki made an intimate study of the disease and were able to differentiate it from encephalitis lethargica and to determine its identity with *Encephalitis B.* In 1924 a very severe epidemic occurred in Japan during a very hot and dry summer season, when 7,000 cases were recorded, with a mortality of nearly 60 per cent. This disease spreads rapidly, in a manner more nearly resembling poliomyelitis, more commonly and more severely attacking those over fifty years of age, in contrast to the relatively mild disease it produces in young people.

During recent years it has also appeared in China, and in the summer of 1938 there was an epidemic in Peking. Most of the cases occurred in children.

Ætiology.—Knowledge of the virus of epidemic encephalo-myelitis comes from Kobayashi, Takaki, Nishibe and Hayashi. Credit is due especially to the latter for his important researches on its transference to monkeys, in which it produces the same histopathological lesions as in man. In America, however, white mice have been found more susceptible than monkeys. Webster and Fite demonstrated that the virus, which is active in the blood and in the central nervous system in the early stages, can be inactivated by convalescent serum.

The transference of the virus from man to man has not been ascertained with certainty, but it has been suggested in China that it is transmitted by mosquitoes, mainly because it is most prevalent during the warmer months when those insects abound. There is also an analogy with equine encephalo-myelitis, which has been observed in horses as well as in man and which is transmitted in this way. Perdrau, by using hyperimmune sera, was able to demonstrate antigenic relationship between the virus of encephalitis japonica and that of St. Louis. The dimensions of the virus particles are estimated as between 20 and 30 $m\mu$.

Symptomatology.—The prodromal symptoms commonly encountered are headache, dizziness, sluggishness, and vomiting. These are followed by psychical disturbances, very often by delusions, but in very severe cases coma ensues, ending in death. The psychical signs and symptoms may be entirely absent in the mild cases, and (in contrast with encephalitis lethargica) meningeal symptoms may predominate. Disturbances of the motor system are characteristic: there are clonic contractions of the muscles which may end in actual convulsions. Fine tremors of individual groups of muscles alternate with attacks of shivering and athetoid movements. The whole muscular tone is increased in the extremities and in the neck and face, especially the masseter muscles, which results in an anxious expression, and ends in trismus making mastication impossible. In very advanced cases, encephalo-myelitis causes paralysis of the spinal cord, but, in direct contrast to encephalitis lethargica, eye symptoms are absent; nor is post-encephalitic Parkinsonianism ever observed, though bulbar symptoms, resulting in failure of speech and difficulty in swallowing, are quite common and, in addition, defects in co-ordination and sometimes even cerebellar disturbances. Anomalies of superficial and deep tendon reflexes are usually present, especially in *spastic* cases. Salivation and excessive sweating are absent.

The foregoing description covers only the main features, however; actually the clinical picture is a many-sided one. There is also another aspect to this disease in that, though the neurological side dominates the picture, there is a secondary affection of the hæmopoietic organs, resulting in a secondary anæmia, which appears to indicate a generalized infection, rather than a local affection of the central nervous system. As a rule, the temperature chart is not characteristic, and the course is afebrile. There are cases, however, in which fever is noted for five to ten days, and these are followed by sequelæ, such as profound neurasthenia. The fulminating cases, which are fatal in twenty-four to forty-eight hours, are generally pyrexial. It is to be noted that there are no pupillary or eye symptoms, and there is no special affection of the bladder or bowels. Usually there is retention at first, followed by incontinence.

Diagnosis.—The main points in differentiation from encephalitis lethargica have been noted. The cerebro-spinal fluid shows all grades of inflammatory disturbance. Kaneko and Aoki have shown that there is an increase of the albumin content from 9 to 350 mgm. per cent. Differential diagnosis has to be made from lymphocytic choriomeningitis.

Pathology.—Epidemic encephalo-myelitis is characterized by diffuse lesions in the brain and spinal cord: these take the form of small white knob-like aggregations of cells, composed of microglia intermingled with lymphocytes and leucocytes. Here and there ganglia cells are also found acutely damaged.

Treatment.—No specific treatment is at present known.

TICK-BORNE ENCEPHALITIS

A somewhat similar, widespread and fatal form of encephalitis has been described and investigated by Pawlowky and his Russian colleagues in Mongolia and Far Eastern territories in the scrubby wastes (Taiga country). This disease has distinct seasonal incidence, and 80 per cent. of cases occur in May and June.

Ætiology.—This form of encephalitis has been shown to be due to a filterable virus transmitted by the bite of a tick (*Ixodes persulcatus*), in which the virus persists, as it is found infective in wild districts uninhabited by man. The virus has been isolated from the brains of various species of wild animals indigenous to the country; these therefore constitute a reservoir of infection. Seasonal incidence of the disease during May and June corresponds with maximum prevalence of *Ixodes persulcatus*. The infection transmitted by bite of the tick is hereditary and therefore larvæ and nymphs are also infective.

Symptomatology.—This form of encephalitis has an abrupt onset and runs a severe course with steep rise of temperature, severe headache, and vomiting. Symptoms of meningeal involvement are followed by signs of focal lesions in the central nervous system, paresis and paralysis of upper or lower limbs or muscles of the neck or back. Parkinsonism never occurs. The case mortality is about 30 per cent.

CHAPTER XXXVI

LÂTAH, RUNNING ÂMOK AND KORO

Latah, a word signifying " nervous " or " ticklish," is not uncommon in the natives of the Malay Peninsula, Java, and the neighbouring islands. It occurs more frequently in women, especially young women, than in men ; children are seldom affected ; it rarely appears before puberty and is especially common at the menopause.

A somewhat similar affliction is described among the Ainu people, usually in women, and is known as *imu*. This manifests as psycho-motor attacks precipitated by some emotional shock. If a sufferer is startled, she may continue to echo everything that is said to her.

Lâtah persists for years. The main characteristics of this state are the same, though there is considerable variety in the intensity of the symptoms. The condition is incurable, shows no tendency to become worse, and does not terminate in insanity.

As the Malays say, an *orang lâtah* never becomes an *orang gila* (âmok). The subjects of " lâtah " at first appear to differ in no way from their neighbours and relations, but on some sudden and striking impression, such as a loud sound, or in response to some overt suggestion by word or deed, they pass into a peculiar mental state in which they involuntarily utter certain sounds and execute certain movements. In other instances they will imitate words or movements, or yield to suggestions from others. During this hypnotic-like state, which may last for a few minutes or longer, the victim is at the mercy of his prompter and will unerringly follow any lead indicated. Although the manifestations of high degrees of lâtah may be followed by exhaustion, or even by swooning, as a rule nothing of the kind occurs. The infirmity is usually discovered by accident. Swettenham, for instance, used to relate that it was only necessary for anyone to attract the attention of these men by the simplest means, such as holding up a finger, or calling them by name in a pointed way, touching them, or looking them steadfastly in the face, in order to make them lose control of themselves and be willing to execute whatever was suggested by a sign. On one occasion, one of them, on being told that a roll of matting was his wife, embraced it with every sign of affection ; but when the other lâtah subject, a policeman, was convinced that the same roll was his wife likewise, he too embraced it, and the two men fell to the ground struggling for the possession of the " lady."

Lâtah folk are favourite subjects for the practical joker, and in a few instances they very much object to being made a show of, and may become dangerous. Lâtah seems to be akin to certain emotional stresses which are common in all barbarous and semi-civilized countries.

Abraham has seen the afflicted, if suddenly startled, fall down and imitate the gestures of anyone in sight ; for instance, an old lady startled by a bicycle bell, will instantly imitate the pedalling of the cyclist till exhausted.

Unless unforeseen accidents occur, lâtah is not fatal. Gimlette and others have called attention to the medico-legal aspects of the disease. Fortunately, examples in which lâtah has been shown to play a part in crime are rare. Temperamentally, all the Malay races are very highly strung and nervous, although externally impassive, and there appears to be an hereditary tendency to the lâtah state in every Malay.

Young-dah-hte is a state closely related to lâtah. Mongolian races are predisposed. Heredity does not seem to play any part. It differs from lâtah in that the patient continuously remains in the imitative condition and is always liable to reactions.

Nat-win-de is a religious dance with closed eyes and swinging movements. It is started by professionals and taken up by others.

There appears to be a somewhat similar affection amongst the Samoyedes which is known as "Ikota," and it is believed that the curious epidemics of religious ecstasy, which swept over Europe during the Middle Ages, were of similar origin.

Banga is a hysterical affliction in Congo women at puberty. The subject is convulsed and rushes about uttering wild cries.

"**Âmok**" (or running âmok) is a term used somewhat loosely for a condition which, in the fully developed form, drives its victims to blind fury and to kill without reason.

Usually the "âmok" runner (or âmoker) has a grievance upon which he allows himself to brood, and after a period of sullenness decides to kill the suspected person and at the same time to destroy as many other people as possible. He therefore arms himself, runs "âmok," and buries his *kris*, when out to slay, in friend and foe alike, with the expectation of being killed in turn.

In other cases there may be premonitory signs in which a person mutters and has delusions. Quite suddenly he will run "âmok" and after the attack may fall into a deep slumber and become comatose. The liability to "âmok" attacks is greatest in the Malays and their drugs, such as Indian hemp (*Cannabis indica*), are known to be potent predisposing causes of the attack. Van Loon found that in Java "âmok" runners are often suffering from some infectious disease, and that the symptoms are hallucinations and confusion; such patients are impelled to flight and attack as reactions to imaginary dangers and the agony and terror caused thereby.

"**Koro**" occurs amongst the Macassars and the Buginese in Celebes, and is also well known among the Chinese as *Shook Jong*, originally described by Blonk in 1895. The term signifies "shrivelling," and a feeling occurs at regular intervals of the penis retracting into the abdomen; if help is not forthcoming the patient dies. In his anxiety, the patient grasps the penis, and if unable to do so, obtains assistance from others. It may be days before the attack subsides, and the sufferer cannot bear to be left alone. If help be not to hand, he will actually tie the penis to his leg with string, anchor it by means of a pin, or may even employ a double-bladed clasping instrument known as *li teng kok*, which is used by jewellers. By the native this tendency is regarded as the "Yin" principle, representing the female power, dominating the "Yang" principle, which represents the male element. In order that a "Yin" disease may be cured, a "Yang" medicine must be employed. The sufferers are generally neurotics, and the anxiety arises out of sexual conflicts. Various pathological conditions, such as œdema of the lower abdomen, hernia, hydrocele and elephantiasis of the scrotum, may evoke fear of an attack. An analogous state, characterized by diminution of the genital labia and shrinkage of the breasts, is known to occur in

Section VI.—TROPICAL VENEREAL DISEASES

CHAPTER XXXVII

LYMPHOGRANULOMA VENEREUM

Synonyms. Climatic bubo; Lymphopathia venereum; Esthiomène; Lymphogranuloma inguinale; Inguinal poradenitis; Poradenolymphitis; Nicholas-Favre disease (French).

Definition.—A type of adenitis of venereal origin, of which the primary lesion occurs on the prepuce or male genitalia. The infection—a filterable virus—causes inflammation and, subsequently suppuration of the inguinal glands. This suppurative state is usually attended by pyrexia and general constitutional disturbance. The bubonic stage occurs in the male, and some think that a general lymphœdema with ulceration, known as esthiomène, represents the analogue in the female. Most authorities also consider that the genito-ano-rectal syndrome and inflammatory stricture of the rectum are due to the same cause.

Epidemiology and geographical distribution.—Scheube originally applied the term "climatic bubo" to a type of adenitis terminating in suppuration, not uncommon in tropical countries. Whether it is becoming increasingly frequent, or whether because attention has been drawn to its peculiar nature in recent years is a moot point, but recently "lymphogranuloma" has emerged from the obscure recesses of textbooks on tropical medicine into the full limelight of general medicine, so as to merit the title of the "*Sixth Venereal Disease,*" which has been bestowed upon it by Stannus.

In tropical practice it is especially prevalent amongst the European crews of warships visiting the coasts of East and West Africa, and is almost equally common in seafaring people (lascars, stewards, and British sailors) throughout the whole of India, China, Malaya, Japan, the Mediterranean, West Indies, and South America.

In 1913, Durand, Nicolas, and Favre described it in France, and possibly the condition long known as the "strumous bubo" is the same.

In 1933 Stannus and Findlay described an indigenous case in England. Since then the Editor has seen several, and more recently Anwyl Davies discovered three more. Now numerous reports of its occurrence in Italy, Rumania, and in fact the whole of Europe, are to hand. In the United States, this disease in all its phases has been discovered, chiefly in negroes. At certain times and places it appears almost to be epidemic. There seems to be no doubt, that, in almost every instance, infection is acquired by sexual intercourse.

Ætiology.—Hellerström and Wassén (1930) originally transmitted the virus obtained from the pus of inguinal buboes to monkeys, intracerebral inoculation producing meningo-encephalitis. The virus, which is apparently contained in the leucocytes, consists of minute particles which can be easily seen, and were figured by Findlay (1939). They can be stained by Victoria blue, Giemsa or Castenêda's method; with Giemsa, the larger bodies take on a bluish-purple tint, while with Castanêda's stain they are reddish-purple. Larger and smaller forms of the virus particles can be demonstrated outside the cells, lying close to cell débris, in compact colony-like masses. When they are within cells the elementary bodies may be found in the cytoplasm of either mononuclear or polymorphonuclear leucocytes. Occasionally, these groups may attain considerable size, forming cyst-like spaces; later, the cyst-wall may rupture. The larger forms have been observed in considerable numbers, chiefly within twenty-four hours of intracerebral inoculation. There therefore appears to be a development cycle of the virus which is complete in forty-eight hours. The virus particles, or granules, were first described in cells from inguinal buboes by Gay and Prieto in 1927, and similar bodies were found by Findlay in 1933. Miyagawa (1938) finally concluded that they represented the virus and gave their measurements as 0·125–0·175 μ, while Findlay, Mackenzie and MacCallum thought that they resemble similar bodies found in psittacosis by Bedson and Bland in 1932.

Intraglandular injection of guinea-pigs with the virus produces an inguinal bubo in almost every case, so that this method may be employed for diagnosis. The most reliable method at present is Findlay's intracerebral inoculation of white mice, which produces encephalitis. Miyagawa found that a chipmunk, *Tamias asiaticus*, is highly susceptible to intratesticular and intracerebral inoculation. The virus can also be cultivated on chick chorio-allantoic membrane in tissue culture. Ravaut, Levaditi, Lambling, and Cachera devised a method of isolating the virus from ulcerative proctitis by inserting a portion of tissue under the skin of a guinea-pig. After a few days, the inguinal gland is excised, emulsified and injected intracerebrally into a monkey. In inoculated mice a characteristic train of symptoms is evolved in five to seventy days, in which weakness, paresis, opisthotonos and convulsions occur. The concentration of the virus in the injected mouse brain is not great, so that dilutions greater than 1 in 1,000 fail to give positive results.

A protection test has been devised, by mixing equal parts of serum of the lymphogranuloma patient with an emulsion of infected mouse brain, diluted 1 in 5 in normal saline, and kept for the night in the ice-chest at 4° C. Doses of 0·5 c.c. injected intracerebrally do not produce encephalitis. The serum of monkeys which have recovered gives the same reaction.

Pathology.—The essential features of the pathology of the human gland consists in little pin-point epithelioid formations scattered all through the gland substance. They are made up of masses of irregularly disposed macrophage cells together with some giant cells. Höppli described localized collections of eosinophils. Subsequently tiny micro-abscesses form.

Symptoms. *Primary sore.*—Durand in 1918, and subsequently Hanschell, described a small herpetiform ulcer on the prépuce which heals in a few days; the adentitis proper does not commence until after the primary lesion has healed. Hanschell believes that the disease does not usually occur in the circumcised. The primary lesion is an erosion with clean edges, and is surrounded by a reddened zone, but with only slight infiltration and induration. The base of the ulcer is usually whitish-grey.

Adenitis.—The incubation period of adenitis is three to four weeks after coitus, but it may be as long as six weeks to two months. The disease generally commences with remittent pyrexia, which may precede the actual localizing signs, and may be mistaken for typhoid. Soon, subacute inflammatory swellings of the groin glands are noted. The inflammation may be unilateral or bilateral; while the oblique glands are most frequently affected, at times the crural glands are attacked. Sometimes one groin is affected after the other. In well-marked cases, the internal iliac glands, sometimes the lumbar glands also, can be felt enlarged and tender on deep palpation. Signs of intoxication from absorption may be widespread, producing prolonged intermittent or remittent fevers, sometimes even pyrexia of 103–5° F. Rigors, vomiting, cyanosis, even slight jaundice, and considerable pain have been noted. Rheumatic-like pains in joints and painful effusions into joint cavities may also occur as a result of absorption. The affected glands slowly enlarge to the size of a hen's egg, or even larger, and after several weeks, it may be months, the swelling gradually subsides (Fig. 104). Usually, the periglandular connective tissues inflame, and the integuments become adherent until suppuration ceases. At other times fistulous tracks form, and continuously exude a clear sticky fluid. The most striking clinical feature in the male is the extensive inflammation of the periglandular tissues with comparatively little pain and suppuration. The following stages are recognized :—

Fig. 104.—Fully developed climatic bubo in right groin, showing also small primary lesion on the corona penis. (*A. H. Walters.*)

(1) A firm solitary gland, with no apparent causative lesion other than a recently-healed ulcer on the genitalia.

(2) A firm solitary gland adherent to overlying skin and deeper tissues. Adjacent glands are enlarged, including external iliac glands, palpable as a mass above Poupart's ligament. The affected glands tend to coalesce.

(3) The glands in the groin soften and fluctuate. If incised, a cavity is disclosed, trabeculated by coarse, fibrous strands.

(4) The softened gland-mass ulcerates through the skin, and spontaneous fistulation occurs. Secondary infection follows.

It was formerly believed that lymphogranulomatous adenitis was unknown in women (Hanschell, 1926), but it is now becoming recognized that typical inguinal poradenitis does occur, though inguinal bubonic manifestations are, on account of the different anatomical disposition of the lymphatic system in the female, comparatively rare; nevertheless, Galloway (1926) recorded his familiarity with typical inguinal buboes in Chinese and Japanese prostitutes in Singapore. Most of the cases of inguinal buboes in women who have given a positive intradermal test (*see* below) have been reported among prostitutes by French writers, though definite evidence of the infection of wife by husband has been obtained in an English case under the Editor's care.

Esthiomène and stricture of the rectum.—Esthiomène is an ulceration of the vulva associated with elephantiasis of the labia, formerly thought to be tuberculous. Stannus and others now believe that esthiomène is the counterpart of lymphogranuloma inguinale in the male. It has been recorded in all the countries of Europe and America, but there are very few references to it among tropical races, though Chesterman on the Congo found typical cases amongst the native women, and also saw the genito-ano-rectal syndrome there. Gray and Yieh, from Shanghai, described four cases in Chinese females. The primary lesion is probably hidden in the posterior wall of the vagina, and the ano-rectal lymphatic gland is the first to be attacked. The infiltration of this gland extends, *via* the lymph-flow, to the anterior part of the vulva, and posteriorly to the rectum, resulting in the *genito-ano-rectal syndrome*, and finally scarring of the glands leads to rectal stricture.

Fibrous stricture of the rectum, in both sexes, is probably due to the same virus. Authorities are now agreed that syphilis cannot be held responsible. Rectal stricture appears to be more frequent in Europeans than in native races, though Maxwell reported it comparatively frequently in China; Gray recorded it in both sexes in Nigeria, and Chesterman on the Congo. Rajam, in Madras, in a clinical study of lymphogranuloma and allied conditions, reviewed 183 cases of poradenitis, and found buboes in 99 males and 2 females, and the genito-anal syndrome in 18 males and 8 females. The virus spreads from the initial site of implantation by the lymphatics to the inguinal and pelvic glands, and later the lymphatics of the anus and rectum become involved, producing at first proctitis and, later still, stricture of the rectum. The following varieties are recognized :—

(1) Anal stricture in women associated with esthiomène.
(2) Annular rectal stricture.
(3) Tubular rectal stricture.
(4) Rectal communicating strictures from ulceration between the rectum, bladder, vagina, prostate and seminal vesicles.

In 1932 Frei reported that 80 per cent. of cases of the genito-ano-rectal syndrome gave a positive intradermal test.

Extra-genital infections.—Extra-genital infections have been recorded on the tongue, followed by glandular enlargements in the neck, by Curth; in the axilla by Hellerström; and on the foot by Lépinay and Grévin. A possible relationship with regional ileitis (Crohn's disease) was suggested by Likely and Lisa; they recorded a case in which multiple granulomata of the ileum were present with frank lymphogranuloma of vulva, vagina and rectum.

Ocular lymphogranuloma.—This was described by Macnie (1941). The whole globe may be covered with granulation tissue and the washings of the conjunctival sac will infect monkeys. Curth and Sanders found that a number of cases of uveitis and kerato-conjunctivitis gave positive intradermal tests; sometimes there is conjunctivitis with ciliary congestion. Fundus changes have been reported, also peripapillary œdema, dilatation and tortuosity of the veins.

Complications.—Sometimes, if too much lymphatic tissue is removed by excision of the glands, an elephantoid condition of the leg and scrotum on the affected side may develop (Fig. 105). This is a grave objection to surgical interference, added to the fact that secondary sepsis is very likely to ensue. Rupture of extensive lymphogranulomatous suppuration into the bladder has been recorded.

Fig. 105.—Climatic bubo two months after incision and circumcision, showing sinus formation. (*H. Wolfe Cowen.*)

Diagnosis.—The diagnosis of climatic bubo and lymphogranuloma inguinale has been placed upon a scientific basis by the introduction of the intracuti-reaction (intradermal test) of Frei (1925), which is now known as the Frei-Hoffmann reaction. The antigen was originally prepared from the inflamed gland tissue.

Frei's method of preparing antigen for the skin test consisted of withdrawing the pus from a gland which has undergone softening, but not fistulation. The aspirated pus is mixed with physiological saline, in the proportion of one part to five parts in a sterile tube, and immediately put up in ½-c.c. to 1-c.c. doses in Jena hard glass ampoules. Thus prepared, it is heated to 60° C. for two hours over a water bath, and the following day at 60° C. for one hour. The antigen should be preserved at a low temperature unexposed to light. Tests must be repeated every three months, and should give negative reactions in skin of normal and control patients suffering from *ulcus molle*. Careful experiments at the

Albert Dock Hospital, London, with a controlled antigen prepared as above, have been satisfactory.

A. H. Walters modified the preparation of the antigen for routine use as follows:

The affected gland, surgically removed, is placed in a sterile glass dish. It is then cut in half and two equal portions are placed in sterile Petri dishes marked 1 and 2. In specimen No. 1 the inner pin-point of necrotic material is macerated in physiological saline and inoculated at once into the inguinal region of guinea-pigs. Specimen No. 2 is macerated in physiological saline in a dilution of 1 in 10 by weight, and then macerated in a water bath at 60° C. for one hour; it is then filtered under strict aseptic precautions through fine Whatman paper in order to remove larger masses.

On receipt of positive animal inoculation results, three batches of antigen are pooled and subjected to further inactivation at 60° C. for one hour on each of two consecutive days. Emulsified brains of mice infected with lymphogranuloma have been employed. These extracts are more easily obtainable and can be standardized, but pseudo-positive reactions occur and may lead to confusion, while reactions may be obtained in normal persons with intradermal injection of normal brain tissue. Rake and his colleagues prepared an extract of lymphogranuloma virus on egg yolk sac. It is known as *lygranum*. When tried out by Sulkin in a series of cases the results were conclusive.

Ottolina (1941) claimed that intradermal injection of 0·3 c.c. of cerebrospinal fluid from a previously proven case of lymphogranuloma gives a positive reaction. The cerebrospinal fluid is concentrated *in vacuo* from 10 c.c. to 2 c.c. before injection.

The Frei Hoffmann test.—The test is carried out on the same lines as the Dick or Schick sensitization tests: 0·1 c.c. of antigen is administered intracutaneously in the forearm, causing a wheal 8–10 mm. in diameter. Physiological saline or *Dmelcos* chancroid antigen is administered on the other forearm as control. A positive result usually appears at the end of 24–48 hours and may vary in size from a circle of 1½ in. in diameter to a considerable reaction about 3 in. in diameter. German writers have noted a hard mass ("*Ein harter Knochen*") of infiltrated skin which may persist for a few days. This never occurs in negative cases.

The Wassén test consists of producing a fatal encephalitis in mice by inoculation of the virus.

The disease must be differentiated from soft sore, filarial adenitis, and plague, especially the ambulant form. In China especially lymphogranuloma buboes have to be distinguished from *pestis minor*; they have also to be differentiated from femoral hernia, but these two conditions may be associated. Tularæmia may also have to be differentiated.

Blood changes.—There is usually a leucocytosis accompanying the suppuration. In the Editor's cases this has invariably been so; the leucocyte counts vary from 8,000 to 27,000, but no cell-type is particularly affected.

Serological changes.—Hyperglobulinæmia is constantly present. The total proteins are between 8·1 and 10·3 per cent. in florid cases. The serum albumin is about 3·9 per cent.; serum globulin 3·9 to 5·6 per cent.

A *complement-fixation* test has been described by McKee and his colleagues. The antigen, *lygranum* (M.L.), stored at freezing point, is made from infected lungs of mice ground up to make a 10 per cent. suspension.

The readings are taken at the end of thirty minutes at 37° C. The lowest initial dilution of serum is 1 in 2.

Treatment.—In the lymphogranulomatous stage the inflamed gland, if discrete, can be excised, and the spread of further mischief appears to be avoided, but surgical interference to lay open the suppurating sinus or remove large masses of lymphatic tissue should be strongly deprecated for, as a result, the gland tissue may become secondarily infected with pyogenic organisms, a permanent lymphatic sinus may form, or chronic lymphatic obstruction may ensue. Usually, excision of the mass when suppuration is present is not followed by clean and rapid healing, but by the formation of sinuses (Fig. 105). Stammers and Law found that surgical removal of the originally infected " feeding gland " may lead to the subsidence of a larger group of secondarily involved glands.

During the acute stage of the disease, treatment should consist of rest and the application of soothing dressings.

Protein-shock therapy is often followed by dramatic results, and the Editor has had considerable experience of this method of treatment. It is especially advantageous when suppuration has commenced, and should be combined with *aseptic aspiration* of the gland. This aspiration may have to be repeated several times.

Typhoid-paratyphoid vaccine (T.A.B.), or " Pyrifer "[1] is employed, commencing with 50 million given intravenously and gradually increasing to 200 or 300 million, injections being given every third day. Two or three reactions are usually required before the buboes dry up and the surrounding induration disappears. This treatment should be combined with rest in bed, and antiphlogistine dressings. When there is active suppuration it is advisable to aspirate, making a small opening with a tenotomy knife, packing with gauze, and using silkworm stitch as a seton.

Vaccine therapy.—The vaccine is prepared by excising a convenient portion of the gland mass, which is cut up into small pieces, dehydrated over calcium chloride, emulsified in saline and injected in increasing doses every second day, but no reliable results have so far been obtained by this method.

Treatment by drugs.—*Tartar emetic.*—Intravenous injections of tartar emetic have been used since 1925. Eight to fifteen injections of from 5 to 10 c.c. of a 1 per cent. solution are required. The pentavalent compounds of antimony—such as neostibosan in recognized doses—have also been employed with apparent success.

Anthiomaline (Lithium antimony tartrate) has been given intravenously or intramuscularly. Stammers and Law commence with a dose of 0·5 c.c. (6 per cent. solution); they increase each dose by 0·5 c.c. up to 2 c.c. twice weekly to a maximum total of 20 injections. Normally only 10 are required. The average length of treatment in first and second stages is about four weeks.

Sulphonamides.—MacCallum and Findlay, by means of chemotherapeutic experiments on the virus of lymphogranuloma in the mouse, have shown that sulphonamides have a definite value. At present it is impossible to say why the virus of lymphogranuloma inguinale alone is susceptible to chemotherapeutic action, while so many other viruses are insusceptible, but the evidence so far obtained seems to point to the fact that living virus may still be obtained from the brains of certain mice after prolonged treatment with sulphonamides.

---

[1] Pyrifer is a *Bact. coli* preparation in strengths from 50–500 million, prepared by Aristopharm Ltd., Switzerland.

In the treatment of the disease in man Montel (1937) in Indo-China found the French preparation, rubiazol, curative, if given in courses over a prolonged period. Earle (1939) reported on the value of sulphapyridine, but recent reports indicate that in actual practice the results are disappointing.

Treatment of rectal stricture.—The treatment of rectal stricture is difficult. Palliative measures consist in dilating by graduated bougies and injecting antiseptic solutions to cure the ulceration. Operative measures depend entirely upon the type of stricture present; Lockhart-Mummery gives the following alternatives: internal proctotomy; complete proctotomy; excision of the stricture or of the rectum; and colostomy. Bensaude and Lambling, on the other hand, consider diathermic dilatation to be the best method, applied for twenty minutes every two or three days, for ten to twelve applications. Oil-soluble local anæsthetics, such as proctocaine, are best for post-operative rectal pain.

The medical treatment of rectal stricture and esthiomène has been improved by the introduction of sulphonamides. Shropshear claimed success with sulphapyridine, in doses of 2 grm. daily, for fifteen days, with a seven- to ten-day interval, after which the course is repeated. Two patients required 108 grm. in two fifteen-day treatments before symptoms disappeared. In women sulphapyridine checks leucorrhœa and heals the ulcers.

CHAPTER XXXVIII

ULCERATING GRANULOMA OF THE PUDENDA

Synonym. Granuloma Venereum.

Definition.—An infective and granulomatous condition of the pudenda, widespread in some parts of the tropics, conveyed by sexual contact and auto-inoculation.

Geographical distribution.—Ulcerating granuloma is widely diffused in India, Guiana, Brazil, West Indies, Porto Rico, Papua, Pacific islands, and Northern Australia; sporadically it occurs in the Southern United States, on the West Coast of Africa, and in Southern China. De Vogel relates that in the southern region of Dutch New Guinea this disease appears in epidemic form and threatens the extinction of the local tribes. In only one case has spontaneous cure been observed.

Ætiology.—There is good reason for believing that the disease is generally, though not invariably, venereal; very rarely, extragenital lesions have been observed. Cleland and Strangman in Australia, Flu in Surinam, and Aragão in Brazil described certain parasitic bodies within the large mononuclear cells from scrapings of the lesions. The organism is like a short bacillus with rounded ends, and measures 1 μ by 0·2 μ; it was described and named *Calymmatobacterium granulomatis* by Donovan, and later by Araujo. Later, this organism was re-studied by E. L. Walker, who considered it to be a capsulated intracellular diplococcus, probably *Bacillus mucosus capsulatus*, one of the Friedländer group. The secondary invader may be the non-hæmolytic anaërobic streptococcus described by Meleney (p. 634).

Dienst and Greenblatt (1943) have not confirmed previous observations, and now think that the Donovan bodies are protozoa, in no way related to bacteria (the diphtheria group). The organism is selective for its particular host, reproduces by multiple segmentation within endothelial cells and is affected by antimony. The bodies are further distinguished by retaining basic fuchsin stain when exposed to weak decolorizing agents. The smear from an ulcer is fixed, flooded with 0·5 per cent. aqueous fuchsin for two minutes, then washed with water and 0·5 per cent. citric acid until the dye ceases to leave the smear (5 sec.). The film is then washed in water and counterstained with 1 per cent. aqueous aniline blue for 5 minutes.

Age and sex.—Ulcerating granuloma has not been recorded before puberty; it has been found only after the age of 13 or 14, and up to 40 or 50. It occurs in both sexes, but more often in women, especially where polyandry is practised.

Pathology.—Histologically this disease is allied to rhinoscleroma, and the close association between these two diseases in Sumatra has been emphasized by Snijders. On microscopical examination the new growth at the margins of the sores is found to be made up of nodules, or masses of nodules, consisting of round cells having large and, usually, badly-staining nuclei. These cell-nests of Malpighian cells are embedded in a delicate fibrous reticulum. An important feature in the histopathology is a peculiar pathognomonic cell described by Pund and Greenblatt (Fig. 106). It is a large mononuclear varying from 25 to 90 μ in diameter, probably derived from a plasma cell. The specific cell, laden with the so-called Donovan bodies, can be shown best by the *Dieterle silver impregnation* method in which these bodies appear as dark brown or black elongated ovoid masses with intense bipolar staining. The nodular masses are, for the most part, covered by epithelium, their under-surfaces merging gradually into a thick, dense, fibrous stroma in which small clusters of similar round cells are here and there embedded. The growths, though very vascular, contain no hæmorrhages; and there are no signs of suppuration or of caseation, no giant cells, and no tubercle bacilli. In vertical section of the small nodules the round-cell mass will be found to be wedge-shaped, the base of the wedge being towards the surface; the deep-lying apex is usually pierced by a hair or two. The growth is found around sebaceous follicles, blood-vessels, lymphatics, and sudoriferous glands; but it is especially abundant, and most deeply situated, around hair follicles.

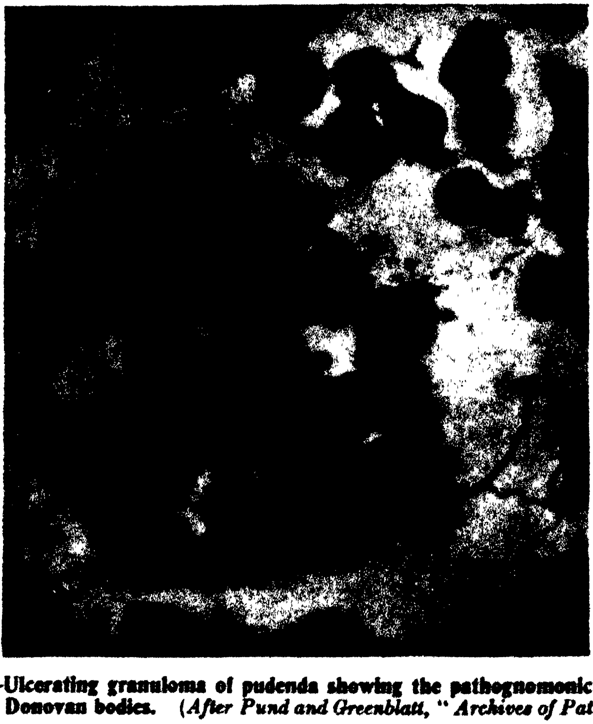


Fig. 106.—Ulcerating granuloma of pudenda showing the pathognomonic cell and contained Donovan bodies. (*After Pund and Greenblatt, "Archives of Pathology."*)

Symptoms.—The incubation period appears to be comparatively short, from two to eight days after sexual contact, but it may be as long as twelve weeks. The disease commences in the great majority of cases somewhere on the genitals, usually on the penis or labia minora, the pubes, or groin, as an insignificant, circumscribed, nodular thickening and elevation of the skin. The affected area, which on the whole is elevated above the surrounding healthy skin, and covered with a very delicate, pinkish, easily-rubbed-off epithelium, excoriates readily, exposing a surface which tends to bleed and break down, although rarely ulcerating deeply. The disease advances in two ways: by continuous excentric peripheral extension, and by auto-infection of an opposing surface. It exhibits a distinct predilection for warm and moist surfaces, particularly the folds between the scrotum and thighs, the labia, and the flexures of the thighs (Fig. 107). Its extension is very slow, years elapsing before it covers a large area. Concurrently with peripheral extension, a dense, contracting, uneven, readily breaking down scar forms on the surface travelled over by the coarsely or finely nodulated elevated new growth which constitutes the peripheral part of the diseased area. Occasionally, islands of active disease spring up in this scar tissue; but it is at the margin of the implicated patch that the special features of the affection are best observed. In cases of long standing the partially-healed areas are covered with thin depigmented skin and thus show up as white patches.

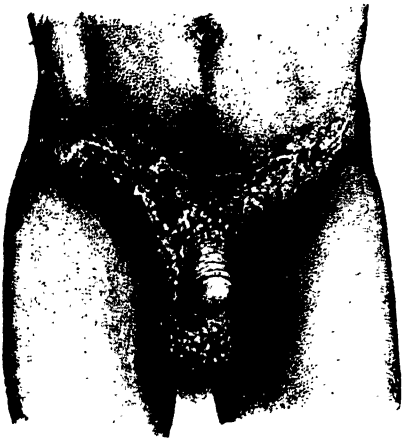


Fig. 107.—Ulcerating granuloma of pudenda in male.

In the female (Fig. 108) the disease primarily attacks the crura of the

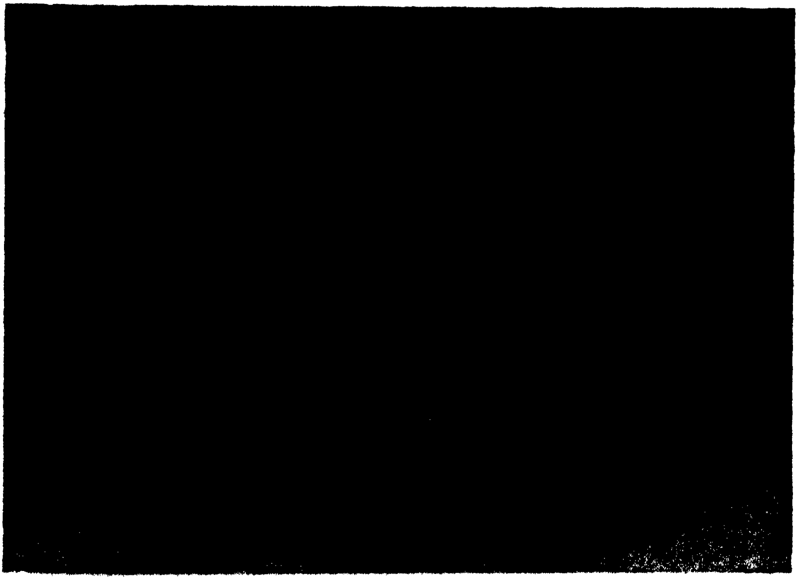


Fig. 108.—Ulcerating granuloma of pudenda in female. Au [illegible]
(Dr. H. Basedow, [illegible]

clitoris, thence extending into the vagina, over the labia, and along the flexures of the thighs. The women thus affected are rendered sterile. In the male the disease may spread over the penis, involve the glans, scrotum, and upper part of the thighs (Fig. 109). Occasionally, the glans penis is not involved. In either sex it may spread in the course of years to the pubes, over the perineum, and into the rectum, the recto-vaginal septum in the female ultimately breaking down. At times, a profuse watery discharge exudes, and even drips from the surface of the new growth, soiling the clothes, soddening the skin, and emitting a peculiarly offensive odour. In this condition the disease, slowly extending, continues for years, giving rise to inconvenience, and perhaps seriously implicating the urethra, vagina, or anus, but not otherwise materially impairing the health. In neither sex do the lymphatic glands become affected. The disease continues entirely local, but in the process of cicatrization the lymph-channels may become blocked, and pseudo-elephantiasis of the genitalia may occur. Impassable strictures of the urethra may result, and recto-vaginal fistulæ are common. It may cause death by eating its way into the bladder, causing septic cystitis, as in a long-standing case under the Editor's care.

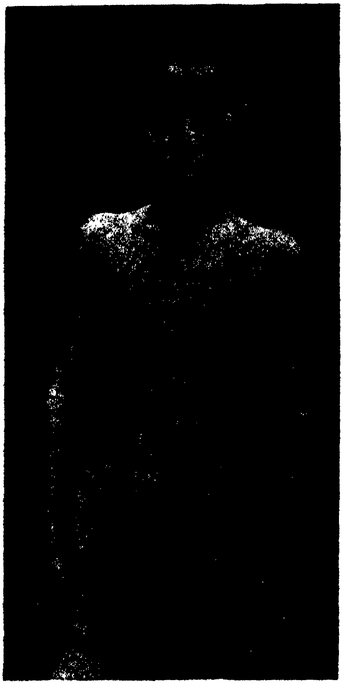


Fig. 109.—Ulcerating granuloma of face and penis in a Chinaman. (*Dr. B. Hawes.*)

Diagnosis.—Malignant and syphilitic ulcerations of the groin are common enough; the disease under notice, however, differs widely from these — clinically, histologically, and therapeutically. It is characterized by extreme chronicity—ten or more years; by absence of cachexia or of any tendency to cause death; by non-implication of the lymphatic system as a whole, and by non-amenability to mercury and iodide of potassium.

The disease which it most resembles is lupus vulgaris. From this it differs inasmuch as it is practically confined to the pudendal region; tends to follow in its extension the folds of the skin; and is not associated with the tubercle bacillus, giant cells, caseation, or other evidences of tuberculous disease. Unless complicated by a coincident syphilitic infection, the Wassermann reaction is negative. The inefficiency of anti-syphilitic treatment soon convinces the physician that the ulceration is not due to this disease. Its characteristic mode of spread suffices to distinguish it from epithelioma and carcinoma. The discharges from ulcerating granuloma have, moreover, a peculiar acrid smell. Pund and Greenblatt described a fungating form affecting the cervix uteri in negresses, which greatly resembles the ulcerative and vegetative type of carcinoma of the cervix. It has also to be distinguished from gonorrhœal endocervitis and from simple erosions.

Treatment.—Scraping and caustics, including the actual cautery, have been freely employed ; but, although some improvement may be effected, new nodules almost invariably spring up in the resulting cicatrix. Until recently, complete excision, where practicable, offered the best chance of permanent cure ; such a proceeding had to be undertaken before large areas and important passages had become involved.

Judging from its relatively superficial nature, and close resemblance to lupus, it seemed probable that ulcerating granuloma might prove amenable to some form of radiotherapy. This is actually the case, and X-rays, originally suggested by Sequeira and Macleod, have been successfully employed in some cases in Madras. Treatment by intravenous injections of tartar emetic, introduced by Aragão and Vianna in 1913, has also proved successful ; improvement usually sets in, and, although in a small proportion of cases relapses occur, in the vast majority the cure is radical. The drug should be injected on alternate days, commencing with ¼ gr. dissolved in distilled water and gradually increasing by the same amount up to the maximum individual dose of 2 gr., but the total amount required to effect a cure varies within wide limits. The Editor had one case with a limited suprapubic lesion which healed completely after a total of 17½ gr., while others required 170 gr. or more. Cicatrization usually takes place rapidly, but indolent ulceration may persist. Apparently stibacetin, neostibosan, stibenyl. and other pentavalent compounds of antimony are more efficacious than tartar emetic. From 3 to 4 grm. of the drugs is necessary. Giglioli, in British Guiana, gave two courses of seven intravenous injections with 45 days between each course. Each injection consisted of 0·1–0·6 grm. of stibenyl (stibacetin) dissolved in 20 c.c. of normal saline. He achieved cures by these means in cases resistant to tartar emetic. On the other hand Earle considered *fouadin* (a trivalent antimony salt) efficacious (*see* p. 686). Stibophen is another similar antimony preparation. The Editor has found it advisable to dress the open granulations daily with an ointment containing 1 per cent.[1] of antimony tartrate in white vaseline. It should be left on the sore for two hours, then wiped off carefully, and the sore washed with boracic solution and dressed with boracic ointment. Intermittent dressing with eusol helps to keep the surface clean. Radiant heat applied to the ulceration has proved beneficial, while touching indolent spots with a silver-nitrate stick will sometimes promote healing. When the sore is of limited extent, excision and subsequent skin-grafting may be advisable, but a wide margin of healthy skin should be removed, or recurrence will most certainly take place. Tartar-emetic treatment may be combined with X-rays and with protein-shock treatment (Hanschell). These shock treatments should alternate with tartar emetic injections. Operative measures, such as the amputation of a badly ulcerated glans penis, may become necessary.

In addition to medicinal means, it is often necessary to open up sinuses and to cauterize undermined margins by the electric cautery.

Many observers have drawn attention to types of ulcerating granuloma which are unaffected by antimony. F. L. Meleney has noted the curative action of *zinc peroxide* in the treatment of anaërobic organisms in acute surgical infections. This preparation had been used since 1903 by French and German surgeons, but for many years fell into disuse. Now it has been applied anew by Meleney in chronic ulcerations due to non-hæmolytic anaërobic streptococci which have hitherto resisted other forms of treatment. The standard preparation of zinc peroxide is one which, when sterilized and suspended in distilled water, consistently yields oxygen while itself remaining soft. It must be rubbed into the wound, especially at its spreading margins, in gangrenous infections of the skin due to synergistic bacterial action, and in undermining burrowing ulcers of the non-gangrenous type.

---

[1] To make antimony-tartrate ointment, the necessary amount of antimony tartrate is first dissolved in a small-quantity of liquid paraffin and then made up to strength with white vaseline. The ointment must not be spread on the healthy skin.

Fig. 110.—Ulcerating granuloma of the pudenda infected with non-hæmolytic streptococcus. (*Dr. Butterfield.*)

To show healing with zinc peroxide treatment and extensive scar-tissue formation.

The liberation of oxygen depends upon the presence of water, and therefore zinc peroxide cannot be employed in oily solutions. The best preparation is that of the Du Pont Chemical Co., Niagara Falls. It must be sterilized at 140° C. for four minutes ; 5–25 grm. are put in large test-tubes, the contents of which are mixed by means of a syringe with enough distilled water to give a homogeneous suspension with the consistency of 40 per cent. cream. It is then spread so as to come into contact with every part of the infected surface, particular care being taken to see that it gets under the undermined skin and into the sinuses, for which purpose it is frequently necessary to use a short catheter. Strips of gauze or silk are dipped into the suspension, and introduced into the sinuses. The dressings should be changed daily, but in painful cases they may be left for two days. The Editor has observed a very serious case successfully treated in this manner when all other measures had failed (Fig. 110). It was also found advantageous to syringe out the sinuses with hydrogen peroxide. All sinuses must be thoroughly opened.

Sulphonamides, especially sulphapyridine, have been successfully employed at this stage. Ross and others recorded success with 3 grm. daily for fourteen days in early lesions. Earle regarded sulphonamides as useful adjuvants to antimony treatment.

Prophylaxis.—As this disease is most certainly spread by sexual connection, prevention consists in the avoidance of illicit intercourse, especially with native women.

Section VII.—TROPICAL SKIN DISEASES

CHAPTER XXXIX

NON-SPECIFIC, BACTERIAL, AND FUNGOUS SKIN DISEASES

I. NON-SPECIFIC SKIN DISEASES

LEUCODERMA, or vitiligo, is extremely common throughout the tropics, and is by no means confined to any particular race. Almost any part of the body may be affected. The atrophied, unpigmented patches of skin slowly enlarge peripherally, and may coalesce. Occasionally the whole body is affected, and a certain amount of symmetry may be observed; the hair of the affected parts may also become white (Fig. 111). The texture and glands of the skin remain normal. The ætiology of the disease is unknown.

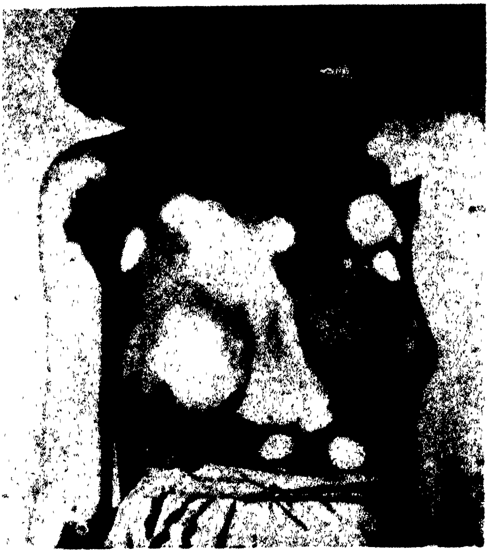


Fig. 111.—Leucoderma. (*Dr. H. K. Giffen.*)

Treatment.—*Bouchi oil* injections have for many years been employed by the Calcutta School of Tropical Medicine. The oil is extracted from the seeds of *Psoralia corylifolia.* Maplestone used it as an injection in conjunction with intestinal antiseptics. The oil is the same as that commonly used for external application. The dose is 0·05 to 0·1 c.c. intradermally at the margins of the patch; the number of injections varies according to its size. After two to three weeks the formation of pigment is noticed, and gradually spreads. A second or even a third series of injections may subsequently be given.

It is possible that cases with a positive Wassermann reaction are syphilitic and may be benefited by antisyphilitic treatment. Care must be taken not to mistake this condition for the depigmentation which is commonly seen in macular leprosy and yaws.

CHELOID

Synonym. Keloid.

The term cheloid is applied to an overgrowth of fibrous tissue in the cellular layers of the corium. Hypertrophic scars are common enough in Europeans consequent upon surgical scars or burns, but some Europeans are predisposed to develop the extensive hyperplasia known as cheloid. Central African negroes are especially liable, and in some tribes cheloidal scars on the back, thigh or chest constitute a readily recognizable tribal mark. Similar fibrosis may occur in these people after a cautery, a healed syphilitic chancre, or even mosquito-bites.

When fully developed, the growth is well defined ; on a white skin it is pinkish or brownish, but it has a distinct red or chocolate tinge on a dark person. Growth takes place very slowly and, rarely, sarcomatous changes may supervene in the fibrous tissue. The growth may cause intense pain or a continuous ache when forming.

Treatment.—The most efficacious method, according to Macleod, is by radium. A full-strength radium plate is screened off by a silver sheet 1mm. in thickness. The exposure should last 18–30 hours. Less brilliant results are obtained by CO_2 snow, especially in early lesions. Electrolysis (3 ma.) is also useful, while occasionally X-rays are satisfactory.

Keloid ought not to be diagnosed as nodular leprosy, but the mistake has been made.

II. BACTERIAL SKIN DISEASES

ULCUS TROPICUM

Synonym. Tropical Sloughing Phagedæna.

Geographical distribution.—Tropical ulcer is common in most tropical countries, particularly in those with a hot, damp climate, principally in the jungle. These sores are often named after the regions in which they are specially prevalent—Mozambique ulcer, Yemen ulcer, Naga sore (Assam), etc.

Occasionally this disease assumes epidemic proportions. Lloyd Patterson described one such epidemic which " swept like a plague up the whole of Assam," seriously interfering with the efficiency of the labour force on the tea plantations.

This form of ulcer was very common among the carriers attached to the East African Force during the 1914–1918 war, and accounted for a considerable amount of invaliding, and among natives in Africa it causes an immense amount of disability. It is the commonest cause of disability amongst labourers in Malaya, the Solomon Islands, New Guinea, and indeed in the whole of Melanesia. The average stay in hospital is 141 days in younger patients and up to 232 days in older ones, so intractable are these ulcers to treatment. In the West Indies, especially in Trinidad, the ulcers are rare in infancy, and Earle stated that they occur after the fifth year and attain their maximum incidence during the third decade. In a mixed community this incidence is highest in Indians. The majority occur during periods of low rainfall and low relative humidity.

Ætiology.—Prowazek attributed these ulcers to *Spirochæta schaudinni*. Although sloughing phagedæna is evidently a germ disease, it is not readily communicated by ordinary inoculation either to man or to the lower animals. Apparently a concurrence of certain unknown conditions is essential. Lloyd Patterson, however, succeeded in producing a characteristic sore by bandaging a swab smeared with discharge from a typical sore on to the surface of an abrasion, from which the scab had been removed.

Sloughing phagedæna is apt to attack the half-starved, malaria-stricken pioneers in jungle lands, over-driven labour gangs, and soldiers campaigning in the tropics. In such circumstances a slight wound, an abrasion, even an insect-bite, or an old chronic ulcer may serve as the starting-point for one of these terrible sores. Where yaws and sloughing phagedæna are co-endemic, the sores of the former may become infected with the virus of the latter, and serious sloughing and cicatricial contractions result. The feet and legs, being most exposed to injury, are the most frequent locations of this form of ulceration; but the arms, or any other part of the body, may also be attacked. The blood-calcium content, blood-sugar and blood-urea are said to be much diminished, probably as the result of deficient dietary (McCulloch). On the other hand, the Editor has observed several severe cases in otherwise healthy and well-fed Europeans in whom a dietetic deficiency could hardly be seriously considered.

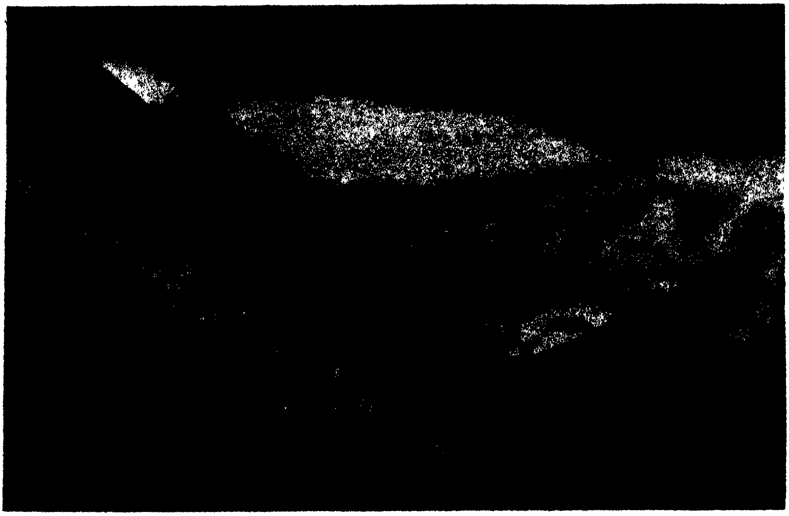


Fig. 112.—Ulcus tropicum.

Clements in Melanesia and James in the Solomon Islands were strongly of the opinion that diet deficiencies (especially B_2), debility and climatic factors combine in predisposing to ulcus tropicum. For instance, the incidence in sago-eaters is vastly greater than in those who subsist on taro. Tropical ulcer is rarer in West African native troops, whose diet includes a ration of red palm oil, than in East African troops, who do not receive this. Some consider that fusiform bacilli and spirochætes play a considerable part in tissue-destruction. A close relationship with chronic malaria appears to be possible in the epidemic form of this disease, and stress is laid upon the importance of Buxton's line of separation between the malarial and non-malarial Pacific islands, which also marks the separation between phagedænic and ulcer-free islands. It is apparently true that the virulence of the organisms responsible for ulcus tropicum is increased by transmission amongst susceptible people.

Symptoms.—If the disease occurs in previously sound skin, the first indication is the formation of a larger or smaller bleb with sero-sanguinolent contents. The bleb may be attended with some pain and constitutional disturbance. When, in the course of a few hours, the bulla ruptures, an ash-grey, moist slough is exposed. The sloughing process rapidly extends in all directions until the skin and subcutaneous fascia over an area of an inch to many inches in diameter are converted into a yellowish, moist, horribly stinking slough. After a few days the centre of the slough begins to liquefy, the sore still continuing to extend at the periphery. In the course of a week or longer the sloughing process may cease and the slough be gradually thrown off (Fig. 112). Then it is seen that not only have the skin and superficial fascia been destroyed, but in bad cases possibly muscles, tendons, nerves, vessels, and even the periosteum of the bones, have shared in the gangrenous process. Fortunately, in many instances, the deeper structures are spared, the disease being relatively limited and superficial. Sometimes, however, important structures, including joints, bones, and large blood-vessels, are destroyed; in such cases, even if life be spared, great deformity may ensue from different forms of ankylosis, or from strangulation of a distal part by a contracting cicatrix, necessitating amputation (Fig. 113).

Diagnosis has to be made from the ulceration of yaws, syphilis, amœbic ulceration of the skin, oriental sore, varicose ulcers, and veld sore, and is usually not very difficult, a final diagnosis being arrived at by exclusion.

Treatment.—As recent observations in Kenya Colony and Tanganyika Territory have shown that dietetics play an important part in the production of ulcus tropicum, it is of the first importance to correct any cachectic state. Thus, good food, fresh vegetables, lime-juice and quinine are almost invariably indicated. Corkhill in the Sudan found that much the same conditions hold there; cod-liver oil dressings, for instance, combined with a liberal vitamin A dietary give good results. Opium in full doses, not merely to assuage pain, but on account of its special action on the phagedænic process, is usually of great service.

If the sore is extensive and septic, the patient should be anæsthetized, and the surface properly scraped and subsequently swabbed with pure carbolic. Directly healthy granulations appear, the ulcer should be treated on general principles. Other authorities prefer strong commercial formalin applied lightly once a day for two or three days, followed by a bismuth paste (B.I.P.) directly a scab has formed.

James stated that ulcers and their complications accounted for most of the deaths in his hospital in New Britain. In serious cases curetting or excision is often necessary, followed by skin grafting, with or without *copper sulphate treatment*. James' method is as follows :

Copper sulphate	1 oz.
Glycerin	2 oz.

Acid carbolic, 1 drm. to oz. of resulting solution.

The copper is crushed, placed with glycerin into an enamel bowl and heated. It is then stirred and allowed to cool and a drachm of carbolic is added to each ounce of solution. The ulcer is gently cleaned with wool swabs, the limb is placed horizontally, and the solution is applied on a piece of wool the size of a pea, the application being continued for two or three minutes. A dressing of acriflavine, 1 in 1,000, on gauze, is applied and is covered by a hot fomentation. The application may have to be repeated twice daily. Most ulcers are clean after applications on two consecutive mornings, and on the fourth morning scarlet-red ointment and adhesive plaster can be applied. A somewhat similar method was advocated by Acton and Panja. Todd praised specially-prepared solutions of potassium permanganate applied on cotton wool to the sloughing floor of the ulcer. The application is continued until pain is produced.

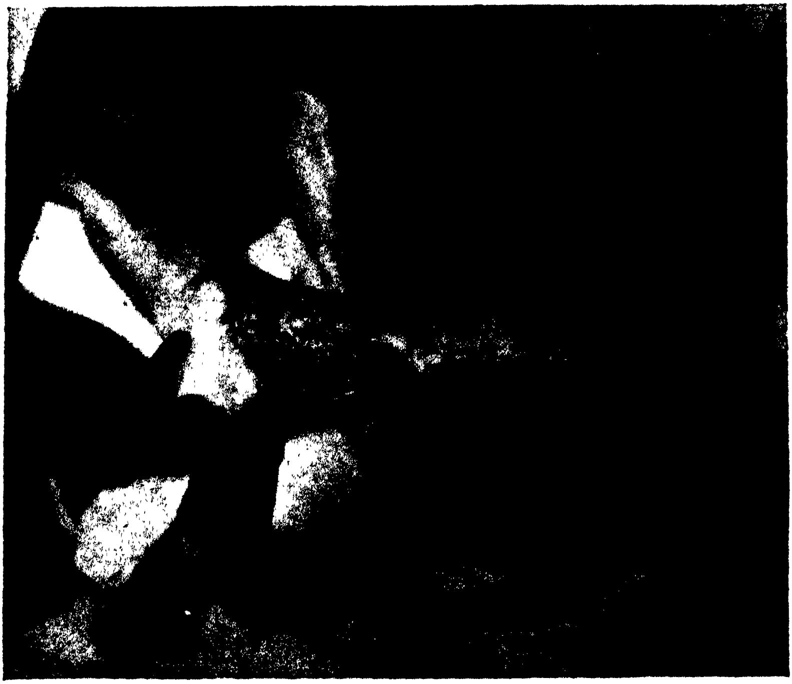


Fig. 113.—Ulcus tropicum : acute case in a European, eventually causing loss of leg.

Harley-Mason in Kenya emphasized the value of tar as an application in the mass treatment of natives, and reported on 300 cases treated in this manner. The ulcer is first swabbed out with eusol, any sloughs present are removed, and the surrounding skin is cleaned. The tar is spread on lint and changed every two or three days. Subsequently, zinc ointment is used; applications of zinc oxide and ichthyol are also recommended. Strocchi first cleansed with hydrogen peroxide and then applied gauze saturated with a preparation of arsenobenzol and iodine known as Neojodo I.C.I. Earle, in Trinidad, used applications of cod-liver and whale oil with success. Sulphonamides are of value in the early ulcers, but scarcely affect those of long standing. Sulphapyridine in daily doses of 3 grm. was found most useful. Douchet used a saturated dressing of sterile ox-bile twice daily. The bile appears to digest the sloughs.

Small superficial ulcers respond readily to powdering with iodoform, or B.I.P. dressing, and subsequent firm strapping with elastoplast after Dickson Wright's method. When elastoplast cannot be obtained, a 3-in. spiral bandage acts well. Sayers in the Solomon Islands found this method particularly suited to the natives of that region. The strapping must be left on for one week. This method is based on the principle that the best dressing for the ulcerated surface is its own discharge. Two longitudinal strips of elastoplast are applied to cover the malleoli, and further longitudinal strips are placed over the instep, over the tendo Achillis, and over the ulcer itself. A circular bandage is then applied, commencing from the toes and winding spirally up the leg. No dressing is used. After twenty-four hours, in a bad case, pus leaks through the bandage and the smell becomes objectionable. Then a plain bandage is applied, and, if the discharge is excessive, the bandage is removed after three days. At this time the ulcer may be larger, but epithelization will be occurring at the edges, and healthy granulations will appear. Spraying with insulin has been found to promote healing at this stage. The leg should then be restrapped and not touched again for a week.

There is another class of case where every simple method fails and the ulcer continues to spread in spite of the most energetic measures. In these cases total excision of the ulcer followed by Thiersch-grafting offers the only means of ultimate success. This method was used by Brennan, Anderson, Roberts in Kenya, and James in the Solomon Islands. By means of a large curved bistoury the whole of the infected tissue is removed. The ulcer is excised under spinal anæsthesia and not scraped. The resulting wound should be dressed with eusol and ointment twice daily until the surface is clean. Afterwards, a dressing of B.I.P. should be applied once daily for some days until it is certain that there is a granulating surface. The site is now treated by skin grafting. According to Enzer, when the Thiersch method fails, "pinch grafting" of small circular patches of whole skin distributed over the area should be employed. It is said that complete healing takes place in fourteen days. The grafts should be dressed with an emollient ointment, *e.g.*, *Tulle Gras Lumière* (Anglo-French Drug Co., 238, Gray's Inn Road, W.C.1). Workers in Kenya agree that the grafts usually take readily, and the stay in hospital after operation is one of twelve to nineteen days.

In contrast to the energetic measures described above, Loewenthal, in Uganda, claimed brilliant results with intravenous injections of calcium. Fifteen grains of calcium chloride in 10 c.c. of distilled water are injected intravenously daily until the cure is complete; the dose is doubled if a case proves resistant. It is said that the offensive odour is lost in the first week, sloughs in the second, and in the third there is a healthy granulating surface with rapidly extending epithelization. However, it is probable that, though disordered calcium metabolism may play some part in the production of these ulcers, yet the results of treatment would be improved by scraping and skin-grafting.

Kerby reported zinc ionization useful in healing up residual areas of ulceration. For this purpose a 1 per cent. solution of zinc sulphate has been used at the rate of 2 ma. to the square inch for 20-30 minutes.

VELD SORE

Synonyms. Septic Sore; Desert Sore; Barcoo Rot.

Geographical distribution.—This peculiar ulceration is widely distributed in the tropics and subtropics wherever desert conditions exist. It has long been known in Queensland and the Northern Territory of Australia. It affected the British troops in the Sudan and South African campaigns, and caused a very considerable amount of disability in Gallipoli, Egypt, Palestine and Iraq during the 1914-18 war. It has also been prevalent in British troops in Palestine, Libya, Abyssinia, Eritrea and the Middle East during the present war. In South Africa it is familiar to sportsmen and travellers.

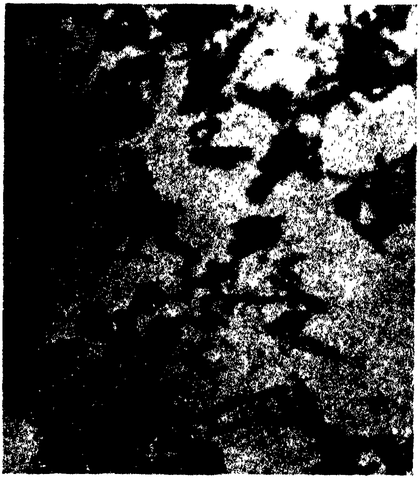


Fig. 114.—Culture of Klebs-Löffler bacillus obtained from the veld sore shown in Fig. 115.
(Dr. H. K. Giffen, Assiut, Egypt.)

Ætiology.—The cause of this condition has long been obscure.[1] In 1916 Craig, in the Sinai Desert, demonstrated the diphtheria bacillus in the lesions. Whether this covers the ætiology of all veld sores cannot at present be affirmed, but that a certain proportion are diphtherial in origin may be taken as established. By sterilizing the surface of the sore with absolute alcohol and scraping the clear surface, a culture of the Klebs-Löffler bacillus was obtained on Löffler's serum. This organism was pathogenic to guinea-pigs and quails, and its lethal effects could be neutralized by injection of antidiphtheritic serum. In the serous contents of the blebs the typical granular bacillus was observed in stained preparations. (Fig. 114.)

The desert sores, as the Editor observed them among British troops, occurred most frequently in men of mounted units, especially those associated with horses and camels, and more recently similar lesions have been found in cavalrymen. The rate of incidence coincides with that of a widespread epidemic of faucial diphtheria. Cameron and Muir (1942) described the lesions as they occurred in mounted units in Palestine in the present war. Acute and chronic stages are recognized. Paralyses occurred in a number of patients in whom there was no other focus of infection than the skin. Not all sores on exposed parts are necessarily diphtherial in origin; some are primary staphylococcal. In Eritrea and Abyssinia it was noted by Louw that the men of mechanical units with oil or grease on their clothing suffered less than others from septic ulceration. Excessive dryness of the skin is a predisposing factor.

---

[1] H. H. Scott (personal communication) isolated the diphtheria bacillus from a veld sore the S. African war in 1901, and succeeded in curing it by application of antidiphtheritic serum.

Symptoms.—The sores occur almost invariably on the exposed parts, mainly those covered by hairs, such as the dorsum of the hand, the fore-arm, the elbows and knee-joints. Sometimes the lesions occur on the face, over the eyebrows and on the cheeks. They may arise *de novo*, or be superimposed on some abrasion.

A regular sequence of events precedes the actual ulceration. At first a *vesicle* full of straw-coloured fluid makes its appearance, generally in the vicinity of a hair follicle; it may vary considerably in size. The pain it occasions is quite out of proportion to the size of the lesion. On bursting it leaves behind a shallow *ulcer* covered with a thin grey pellicle. The raw ulcerated surface is exquisitely tender, and it may continue to spread peripherally. (Fig. 115.)

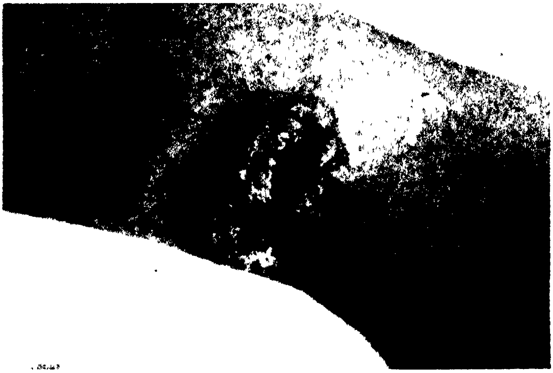


Fig. 115.—Veld sore on leg containing growth of Klebs-Löffler bacillus.
(Dr. H. K. Giffen.)

After the inflammatory changes have lasted two or three weeks the ulcers enter upon a *chronic stage*. At this stage they are characteristic in appearance and perhaps are more familiar to practitioners than the incipient stages. The ulcers are punched-out, circular, with undermined edges and thickened margins; their base is covered with grey-coloured and scaly débris, beneath which can frequently be distinguished an adherent membrane, but little or no pus is discharged. The peculiar ulceration which results is most intractable, and resists all external forms of medication; the edges become indurated, and the thickened tissue has a cyanotic appearance. In sores in which healing does take place, a thin paper-like scar remains for several years. The actual ulceration may continue for two years or longer.

The Klebs-Löffler bacillus can be isolated from the primary lesions; from the chronic ulcerations it is recovered with difficulty, being overgrown with staphylococci and other organisms of suppuration. The best medium is Marshall tellurite.

Diphtheritic pareses, or paralyses, have been observed in association with these sores; in one series this complication occurred in 27 per cent. Paralysis of the palate, arms and legs, and accommodation paralysis of the iris have been observed. There may be ataxia, loss of knee-jerks, anæsthesia and in ordination, recalling at first sight locomotor ataxia or beriberi. Walshe pointed out that the initial local paresis is in anatomical relation to the site of the infective focus, and may be taken to indicate direct passage of toxins from the diphtheritic lesion along the neural channels to the central nervous system. Accommodation pareses, on the other hand, usually appear in the second week, no matter what the site of the local lesion may have been. Polyneuritis is usually delayed for three weeks or longer.

Treatment.—The specific treatment for this kind of ulceration is anti-diphtheritic serum, which has a very striking effect in healing up ulcers that have persisted for a year or even longer. At least 20,000 units should be given, and should be injected subcutaneously or intramuscularly in the vicinity of the sores. In the present war, sulphonamides by the mouth have been found useless, but in chronic cases staphylococcal vaccines are advocated, together with compresses of hypertonic saline, cod-liver oil dressings, and elastoplast bandages. In some cases silver nitrate stick is beneficial.

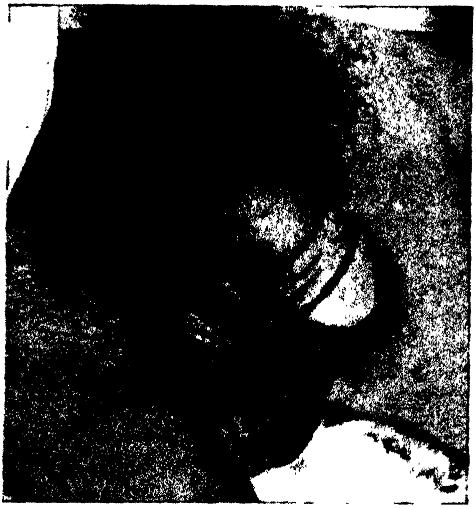


Fig. 116.—Veld sore. Primary lesion on adductor aspect of thigh; secondary contact sore on scrotum.
(*Capt. Manton, A.D.C.*)

In staphylococcal sores sulphonamide paste and acriflavine ointment have been employed (acriflavine, 0·1 per cent.; adeps lanæ anhydrous 45 per cent.; water 100 per cent., to which is added 10 per cent. *sodii sulph.* for osmotic effect).

Prophylaxis.—Protection of exposed parts of the body, especially the knees, against abrasion in desert regions where these sores occur, is obviously indicated. Mounted men should wear knee-breeches and should not be permitted to ride in shorts. The application of antiseptic lotions to any abraded surface at the earliest possible moment is also indicated. As there is some evidence that dried horse-manure may act as a nidus of the bacillus, care should be taken to avoid contact with this as far as possible.

BOILS

The anatomical and clinical features of this painful affection are too familiar to require detailed description. Suffice it to say that a boil is produced by the proliferation of *Staphylococcus pyogenes aureus* and *albus*, *Streptococcus pyogenes*, or other pyogenic micro-organisms in the skin and subcutaneous tissue; that the organisms give rise to local and limited infiltration of the tissues with lymph, leading to necrosis, the central core being surrounded by an areola of acute inflammation; that this core is separated by a process of sloughing and so got rid of, the resulting ulcer speedily healing, and leaving a depressed scar which, when occurring about the legs, may become pigmented. Though a self-limiting disease locally, it is nevertheless capable of being inoculated elsewhere in the same individual, both through a breach of surface and also by simple contact of the discharges with the skin, the micro-organism apparently entering by a hair follicle. This auto-inoculability of boils is apt to be overlooked.

Conditions of debility, presumably by lowering resistance, predispose to boils; the subjects of diabetes are especially liable to them, the saccharine state of the blood or secretions seeming to be particularly favourable to growth of the specific germ. In the tropics, boils are the frequent accompaniment of and sequel to malaria.

Treatment.—Boils ought never, unless in very exceptional circumstances, to be poulticed. Poulticing, although it may relieve the pain of the existing boil, is apt to be followed by more boils in the area made sodden by the heat and moisture. Nor should boils be incised or squeezed. The only exception to the rule of not cutting is a boil in the scalp or axilla. In the former situation, unless opened early, they are apt, especially in young children, to burrow and cause troublesome abscesses; in the latter situation boils tend to be very indolent and painful, and do not readily break through the lax integuments.

In any situation in which the boil is likely to be irritated by pressure or clothing, it is sometimes a good plan to cover the part with a circle of wash-leather spread with soap plaster and having a small hole cut in its centre corresponding to the apex of the boil or, under modern conditions, with a specially-prepared elastoplast strip. When a boil opens, the discharge must be kept from soiling the adjoining skin, and the patient must be warned against touching the skin elsewhere with pus-soiled fingers. The parts must be frequently cleansed with 1 in 1,000 corrosive sublimate lotion, powdered with boric acid, and covered with a dry, absorbent antiseptic dressing. A threatening boil may often be aborted by touching the little initial itching or vesiculated papule with some penetrating antiseptic, such as iodine tincture, or by painting it with collodion. A very successful method is to drill slowly into the centre of the papule with a pointed pencil of hard wood dipped in pure carbolic acid. The point of the pencil should penetrate at least an eighth of an inch, and should be frequently recharged with the acid during the drilling process; the pain is trifling. In this way, in a severe attack of furunculosis, boil after boil may be aborted and the attack brought to an end. In obstinate chronic furunculosis excellent results have occasionally attended treatment by injections of an autogenous vaccine commencing with a dose of fifty millions and working up to three hundred millions of organisms.

The effect of various sulphonamides and penicillin on pyogenic suppuration is now being noted.

In sulphathiazole, given in full doses of 3 grm. per diem, we possess a specific for some cases of staphylococcal suppuration.

PEMPHIGUS CONTAGIOSUS (PYOSIS MANSONI)

Geographical distribution.—Pemphigus contagiosus is very common in

South China during the hot weather; in some years it may even be described as epidemic. It is perennial in the Straits Settlements, and it is known in Ceylon, Madras, in North Queensland, Japan, and America. European are more liable to it than native children; European adults are by no means exempt, but the native adult is rarely affected.

Ætiology and pathology.—Like impetigo contagiosa, this is undoubtedly a germ disease, caused by streptococci and staphylococci. Manson originally found a diplococcus in epidermis and in the fluid of the blister.

Symptoms.—Pemphigus contagiosus closely resembles certain forms of the impetigo contagiosa of temperate countries, and is probably a variety. The individual lesions, as can readily be ascertained by inoculation experiments, begin as minute erythematous specks, which rapidly proceed to the formation of vesicles, bullæ, or even large pemphigus-like blisters.

Pemphigus contagiosus may occur in almost any part of the body. In young children it is usually diffuse; in adults it is mostly confined to the axillæ and crutch.

Diagnosis.—Absence of constitutional symptoms, or of a history of such, distinguishes pemphigus contagiosus from chickenpox. Absence of trichophyton elements, and of a well-defined, slightly raised, festooned and itching margin, together with the presence of large blebs and scaling of the epidermis, distinguishes it from ordinary forms of body ringworm—a disease with which, when occurring in the armpits and crutch in adults, it is frequently confounded.

Treatment.—Cleanliness, the frequent use of a corrosive sublimate lotion (1 in 1,000) and a dusting-powder of equal parts of boric acid, starch, and zinc oxide, or ammoniated mercury ointment are specially effective. Sulphonamide compounds, especially sulphapyridine in full doses of 3 grm. daily to an adult, were found effective by Earle. In the school and nursery those responsible for the care of children must be informed of the contagiousness of this unpleasant affection, and measures must be instituted accordingly.

Craw-Craw and Ulcerative Dermatitis

Synonym. Nodular Dermatitis.

Symptoms.—The term craw-craw is very loosely applied. Emily described under this name a papulo-pustular skin affection which is common in certain parts of tropical Africa and is often the cause of much suffering to the traveller. It, or a similar disease, is by no means confined to Africa, for it is seen in patients from Ceylon and India, and Manson was at one time very familiar with it in South China. The disease begins as an itching papule, very possibly at the seat of a mosquito-bite. The itching provokes scratching, whereby some form of pyogenic micro-organism is inoculated. Pustulation follows, and is spread over feet and legs by soiled shoes and stockings, and by auto-inoculation. In this way an ulcerating, pustulating dermatitis is kept up.

In the exudate of these papules O'Neil originally found small filaria embryos which resembled the embryo of *Acanthocheilonema perstans*. Brumpt did not believe that these are examples of the embryos of *Onchocerca volvulus*, as was affirmed, but possibly they are the same as the microfilariæ described by Macfie (*see* p. 938).

Diagnosis.—The hard, horny papules of craw-craw have to be differentiated from scabies, which is common in African natives. They have also to be distinguished from the lichenoid eruptions caused by microfilaria volvulus (p. 741).

Treatment.—Emily described a very efficient treatment. Pustules are opened, crusts removed, and ulcers scraped. Boric-acid powder is then dusted freely on the parts after a thorough scrubbing with sublimate lotion (1 in 1000); borated vaseline is applied on lint, and this is covered by absorbent cotton and a bandage. The dressings are not disturbed for a week, when the parts will be found soundly healed. Similar auto-infective diseases, so common in the tropics, may be treated by prolonged soaking in a warm carbolic-acid lotion (1 in 20), followed by dry dressing with boric powder. Infected slippers, shoes, and stockings should be destroyed.

III.—PARASITIC DERMATITIS

CERCARIAL DERMATITIS (SCHISTOSOME DERMATITIS)

Cort in Michigan (U.S.A.) in 1928 drew attention to a special kind of dermatitis produced by *Cercaria elvæ*, and *C. douthitti* was soon afterwards found to cause similar lesions. In England and Wales dermatitis after bathing in ponds and reservoirs has been noted by Matheson, Taylor and Baylis as due to *C. ocellata*, a form closely allied to *C. elvæ*. The cercariæ burrow in the skin, where their heads become arrested and cause a pustular eruption. All these cercariæ are derived from different species of snails, especially *Lymnæa ocellata*. *C. elvæ* and *C. ocellata* are large cercariæ nearly 1 mm. in length overall, twice that of the bilharzia cercariæ; the tail is bifurcated and all possess two suckers. Cercarial dermatitis is commonly known as "sedge-pool itch" or "swimmer's itch," and takes the form of an itching maculo-urticarial dermatitis, later becoming papular or pustular; it may be, after a few days, actually exanthematous. It is always connected with paddling or swimming in infected waters a few days previously. A somewhat similar dermatitis is noted in association with cercarial penetration in *Bilharzia hæmatobia* and *B. mansoni* infections.

IV.—ALLERGIC AND TOXIC DERMATITIS

PYRETHRUM DERMATITIS

Pyrethrum dermatitis has been noted in Kenya, and is caused by the leaves and flowers of *Chrysanthemum cinerariafolium*, which grows at altitudes of 500–7000 feet and flowers throughout the year. The pyrethrum content is 1·2 per cent. Absorption is facilitated by constant sweating, and exposure to sunlight greatly exacerbates the lesions. Some persons on contact exhibit merely a local dermatitis; others show a widespread allergy. Itching commences at the corners of the eyes, and is followed by lachrymation, an irritating vesicular rash, peeling of the skin, and formation of painful fissures.

POISON IVY DERMATITIS (DERMATITIS VENENATA)

Many tropical plants cause dermatitis which may assume an erythematous, vesicular or urticarial form. Intimate contact with the plants or its leaves is necessary. Poison ivy (*Rhus toxicodendron*), poison sumac (*R. vernix*), poison wood (*Metopium toxiferum*) in North Eastern and Southern United States cause intense dermatitis. Repeated attacks do not produce immunity. The venom is *toxicodendrol*. Treatment consists of washing the skin with soap and water; alcoholic or oily solutions must be avoided. Clothes must be decontaminated by immersion in 1 per cent. calcium hypochlorite for twenty minutes.

OTHER FORMS OF DERMATITIS

Several other plants and flowers may cause severe allergic dermatitis, such as cypripedium (lady's slippers), *Euphorbia*, primroses, lilies and vanilla beans; sometimes also mangoes and, in Japan, lacquer made from *Rhus vernicifera*.

Iroko dermatitis.—Idiosyncrasy to wood dust is not uncommon. Iroko is a trade name for *Chlorophora excelsa*, a tree of East and West tropical Africa, and known as African teak. The dust produces the usual signs of allergy, with skin irritation, œdema of face, blepharospasm, acute coryza and pharyngitis. Other woods, such as satin wood, teak and mahogany, also produce allergy in susceptible persons.

V.—CLIMATIC SKIN DISEASES

PRICKLY HEAT

Synonym. Climatic hyperidrosis.

Prickly heat, or, as it is sometimes called, lichen tropicus, is probably a form of miliaria (not of lichen) connected with the excessive sweating incident to the heat of tropical climates in association with high humidity. It therefore occurs especially in the Red Sea, Persian Gulf, the plains of India, in Eritrea and Somaliland; in the New World, in Panama and in northern parts of South America.

Ætiology.—According to Pollitzer, the mechanism of its production depends on the non-cornification of the cells of the stratum corneum, the individual cells of which, in consequence of being sodden by constant perspiration, swell, and so obstruct the orifices of the sweat-glands, thereby leading to accumulation of sweat in the ducts. The blebs and bullæ are due to breakdown of function in the second form of sweat glands of the skin, especially the large coil sweat glands localized to the axillæ and genital regions. The miliary rash, commonly known as prickly heat, is due to dysfunction of small sweat glands, and a pemphigoid condition due to dysfunction of the large sweat glands.

In scales obtained from the lesions, E. C. Smith demonstrated yeast-like budding forms and branching mycelium of a species of Oidium, but this probably represents a secondary infection.

Symptoms.—Many Europeans in the tropics suffer from prickly heat, particularly during the earlier years of residence. Some never seem to become acclimatized, but continue year after year to exhibit their crop of prickly-heat lesions when the hot season comes round.

Though sufficiently annoying in the robust and healthy, prickly heat is not a grave affair. It is otherwise in the invalid, delicate sickly children, hysterical and, especially, parturient women; to these it may prove, by interfering with sleep and provoking restlessness, a very serious matter.

Prickly heat consists of a miliary-like eruption, generally most profuse on those parts of the body, as around the waist, which are closely covered with clothing; but it also occurs on the backs of the hands, on the arms, legs, forehead, occasionally on the face, the scalp, in fact on any part of the surface of the body except the palms and soles. The minute, shining, glass-like vesicles, and the numerous, closely-set, slightly inflamed papules, give the skin a feeling of being thickly sprinkled with grains of sand. The eruption may continue for months on end, becoming better or worse according to circumstances. The pricking and itching are often exceedingly distressing. Anything leading to perspiration immediately provokes an outburst of this almost intolerable itching—nothing more certainly than a cup of hot tea or a plate of hot soup. Long drinks, exposure to the hot sun, close rooms, warm clothing, all aggravate the distress. As soon as the weather becomes cool the eruption and the irritation quickly subside.

Blomfield (1943) divided the forms of prickly heat clinically into (1) miliaria, (2) multiple boils, (3) impetiginous, (4) pemphigous, (5) pustular with fungous infection. A special and distinct form of boil develops, consisting of insidious, painful blisters, especially on the fingers. These are deep-seated whitish swellings, very often with paronychia. An impetiginous rash is a frequent concomitant infection.

A very severe form consists of very painful symmetrical crops of blebs and bullæ in armpits and crutch. The bullæ are filled with thin pus, and are surrounded by a bright red ring of acute inflammation.

The pemphigoid state is a late stage of the disease, and is often complicated by secondary fungous infection.

Treatment.—Manifestly, the most important thing is the avoidance of all causes of perspiration—particularly the copious consumption of fluids, especially hot fluids—moderation in exercise, avoiding sea-bathing, close rooms, warm clothing, and so forth. A towel should be carried to mop up sweat. The sleeping-mattress and pillow should be covered with a finely woven grass mat, and the bed provided with what is known in the East as a " Dutch wife "—that is, a hollow cylinder, 4 ft. by 8 or 10 in., of open rattan work, over which the arms and legs can be thrown, and unnecessary apposition of sweating surfaces so avoided. A punkah at night is a great comfort. Afridol soap, containing oxymercuriotoluylate of sodium, in which mercury is in non-ionizable form, can be recommended as a preventive and a curative measure. The soap is powerfully germicidal and should be used twice daily with warm water. A firm lather should be produced in warm water and applied to the affected parts. The lather should be left to dry on the skin for a quarter of an hour so that it can exercise its full effect, after which time it can be thoroughly washed off. When this is unprocurable, hydrarg. perchlor., 1 in 1000 solution, may be used, followed by boric acid, calamine and zinc oxide in equal parts as a dusting powder. Midgley's " Medisoaps " are also recommended, especially one containing 20 per cent. carbolic acid, and a second containing mercury biniodide. Every bathroom in the tropics should be provided with some mildly astringent and antiseptic dusting powder. A very good one consists of equal parts of boric acid, oxide of zinc, and starch. This should be freely applied, after careful drying of the skin, particularly to the axillæ, the crutch, under the mammæ in women, and between the folds of skin in fat children and adults. A simple precaution of this sort saves much suffering both from prickly heat and from epiphytic skin disease. Ruge recommends rice powder containing a little *desitin*.

The frequent application of a salicylic-acid (1 dr.) and spirit (8 oz.) lotion has been advised. Pearse strongly recommends the inunction of a mixture of almond oil and lanolin in the proportion of 8 to 1. Some consider thin flannel a better wear than cotton or linen as a preventive of prickly heat. Sometimes the following powder, gently rubbed in for five or ten minutes with a damp sponge, will cure bad patches: sublimed sulphur, 80 parts; magnesia, 15 parts; oxide of zinc, 5 parts. Calamine lotion, with or without hydrocyanic or carbolic acids (2 per cent.), relieves the itching and is strongly recommended.

TROPICAL CHEIROPOMPHOLYX

This name is given to vesicular eruptions on the hands, fingers or feet.

In the majority of cases these are due simply to eczema ; others are signs of dermatitis due to external irritants, or are toxic eruptions due to ringworm infection of the toes. Owing to the thickness of the horny layer on the hand, the vesicles cannot rupture as they would elsewhere, and remain in the skin for days like grains of boiled sago. The best treatment is calamine and lead lotion with liquor picis carbonis, and sometimes the addition of weekly doses of a quarter of a pastille of X-rays, not more than four in all.

It is claimed by Fitz-Patrick that a distinct form, endemic in tropical Africa and India, is caused by an anaërobic bacterium which attacks the palmar and interdigital aspects of the hands and the plantar aspects of the feet. The following ointment is said to be specific :

Coal tar	3 parts
Powdered charcoal .	1 part
Zinc oxide . .	4 parts
Lanolin and vaseline	12 parts

The ointment is rubbed well into the affected parts, and cotton gloves or socks are worn. In conjunction with this, resorcin soap must be used.

VI. FUNGOUS SKIN DISEASES

Dhobie's Itch (Tinea Cruris) and Pityriasis Versicolor

Ætiology and nomenclature.—By the lay public all epiphytic skin diseases in the tropics—more especially all forms of intertrigo— are spoken of as *dhobie's* (washerman's) *itch*, in the belief, probably not very well founded, that they are contracted from clothes which have been contaminated at the washerman's. There are many sources of ringworm infection in warm climates besides the much-maligned dhobie.

In the tropics, native children often exhibit dry, scurfy patches of ringworm on the scalp ; and the skin of the trunk and limbs of adults is not infrequently affected with red, slightly raised, itching rings, or segments of rings, of trichophyton infection. In some cases these rings enclose areas that are many inches in diameter.

Pityriasis versicolor (*Tinea versicolor*) is also very common in the tropics. It is the usual cause of the pale, fawn-coloured, slightly scurfy patches so frequently a feature of the dark-skinned bodies of natives. On the dark-pigmented skins of negroes, Indians and dark-complexioned Chinese, the patch of pityriasis—unlike that in Europeans and light-skinned Chinese—is usually paler than the healthy integument surrounding it. The pigment in the fungus and the profuse growth of the latter conceal, as a coat of paint might, the dark underlying natural pigment of the skin, which, moreover, in certain cases seems to be affected (either increased or decreased) by the action of the fungus. The disease is most commonly seen in young adults, is favoured by excessive perspiration, and especially by flannel underwear, and is rarely seen in the aged.

Several varieties of fungi may be involved in the production of pityriasis; besides *Malassezia furfur*, the best-known is *M. mansoni*, of which a culture in maltose-agar produces black hemispherical colonies, black patches on the affected skin. The mycelium and spores are refractile with slow budding. The *hyphæ* are 2–3 μ, the spores 3–8 μ.

The expression dhobie's itch, although applied to any itching, ringworm-like affection of any part of the skin, most commonly refers to some form of epiphytic disease of the crutch or axilla. This infection has now become widespread in Great Britain and is endemic in many English public schools, where it is spread by infected clothes and water-closet seats. There are at least two species of parasite which in the tropics are apt to attack those situations, namely a trichophyton—*Epidermophyton inguinale*—and *Actinomyces minutissimum* of erythrasma.

E. inguinale is peculiar to man only; it is not easily cultivated, and grows slowly. On Sabouraud's agar medium it takes a week to develop, and appears first as powdery growth. The mycelium is 1 μ in diameter, often fragmented into bacillary arthrospores.

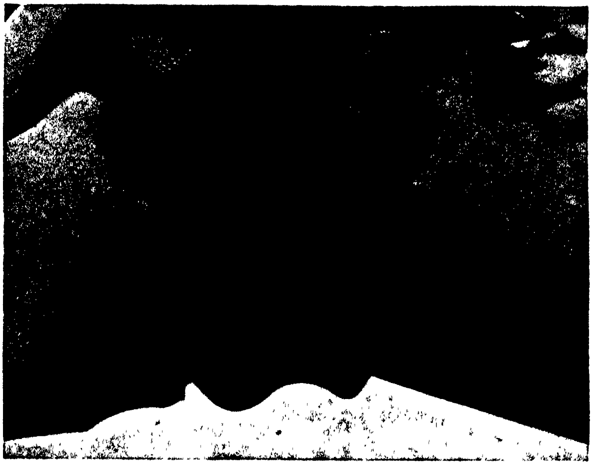


Fig. 117.—Dhobie's itch, symmetrical lesions in groins.

Symptoms.—The suffering to which certain forms of dhobie's itch give rise is often severe. In hot damp weather, especially, the germs proliferate actively, producing, it may be, smart dermatitis. The affection begins usually as slightly raised, rounded and elevated papules which spread peripherally, producing a raised festooned border covered with thick scales. The excessive irritation thus set up leads to scratching and, very likely, from secondary bacterial invasion, to boils or small abscesses. The crutch, or axillæ, or both, are sometimes rendered so raw and tender that the patient may be unable to walk or even to dress. (Fig. 117). It commonly extends backwards on the perineum and into the natal cleft about the anus. It often affects the skin under pendulous breasts and occasionally forms patches resembling tinea circinata on the thighs. The irritations thus produced are usually worse at night, and may keep the patient awake for hours. Even without treatment, when the cold season comes round, the dermatitis and irritation subside spontaneously. The affected parts then become dry, pigmented, and scurfy, and the fungus remains quiescent until the return of the next hot weather.

Diagnosis.—The diagnosis of mycotic dermatitis is usually easily made. the festooned margin is almost conclusive. If doubte xists, the microscope may be necessary ; but, owing to the inflamed condition of the parts, there may be much difficulty in finding fungous elements, even when the case is certainly epiphytic. A negative result is, therefore, not always conclusive against ringworm. The mycelial elements can be distinguished in epidermal scales soaked in liquor potassæ. It has to be distinguished from *seborrhœic dermatitis, intertrigo* and *flexural psoriasis.*

Treatment.—The patient should get two pairs of running shorts, which should be worn on alternate days, the pair not in use being boiled. After a thorough use of soap and water, the application of *Vleminckx's solution* of sulphide of calcium (1 oz. quicklime, 2 oz. precipitated sulphur, 15 oz. water, boiled together in an earthenware vessel till reduced to 10 oz. ; the clear sherry-coloured fluid being decanted after subsidence) every night for three or four nights generally brings about a rapid cure. If the parts are inflamed and tender, the solution should be diluted to half- or quarter-strength for the first two applications. A preliminary soothing treatment by lead lotion, or an ichthyol or hazeline cream, is desirable in such cases. A tincture of the leaves of *Cassia alata* painted on, or vigorous rubbing with the crushed leaves themselves, is equally successful. If these fail, chrysophanic acid ointment, 20 gr. to the ounce of vaseline, rubbed in twice a day until a slight erythema shows at the edge of the diseased patch, is almost invariably successful. When prescribing chrysophanic acid the physician must be careful to inform the patient of its staining effect on clothes ; to warn him to stop its use as soon as the erythematous ring shows, and to be careful not to apply the ointment to the face.

More conveniently, chrysophanic acid may be prescribed in the following form with gutta-percha, and should be painted on with a brush on alternate nights.

Acid. chrysophan.	gr.xx	(1·296 grm.)
Chlorof.	ʒi	(3·5 c.c.)
Liq. gutta-perchæ	℥i	(28·42 c.c.)

Cignolin is a synthetic chrysarobin and is useful in all fungoid skin affections, in fungus of the nails, cheiropompholyx, and in psoriasis. Cignolin is apparently free from toxic action on the kidneys, and in neat concentrations it can be applied to the scalp without any danger of conjunctivitis. The prescription is cadojel (a proprietary tar preparation), 1 grm. ; cignolin, 0·1–0·2 grm. ; benzol, 10 grm. If cadojel is not obtainable, a suitable formula is :

Ol. cadin (deod.)	♏xl	(2·368 c.c.)
Cignolin	gr.iv	(0·259 grm.)
Benzol. rect.	℥i	(28·42 c.c.)

The combination of cignolin and tar follows the indications closely, for the former has a parasiticidal action and the latter is unrivalled for its soothing properties.

The method of application is very simple, the affected areas being painted with the solution twice daily and then covered with strips of gauze. If there is too much irritation, then the painted areas are further protected with a thin layer of Lassar's paste or calamine lotion.

The following are the other prescriptions of Cignolin which may be used for this or any other fungus affection.

1. Cignolin	gr.x	(0·648 grm.)
Chlorof. meth. ad . . .	℥i	(28·42 c.c.)
Ft. sol. = Cignolin paint.		
2. Cignolin	gr.iv	(0·259 grm.)
Zinc oxid.	ʒss	(1·944 grm.)
Ol. oliv. ad	℥ss	(14·21 c.c.)
Ft. unguentum.		
3. Cignolin	gr.ss	(0·032 grm.)
Liq. carb. deterg. . . .	ʒss	(1·176 c.c.)
Acid. salicyl.. . . .	gr.iii	(0·194 grm.)
Paraff. moll. ad . . .	℥ss	(15·55 grm.)
Ft. unguentum.		
4. Cignolin	gr.v	(0·324 grm.)
Ichthyol	ʒss	(1·944 grm.)
Paraff. moll. ad . . .	℥i	(31·1 grm.)
Ft. unguentum		

Hallow (1936) endorsed the value of cignolin treatment in his account of 310 cases treated in this manner. The patient should be isolated and kept in clean pyjamas during treatment. For three days cignolin, 2 per cent. in soft paraffin, is applied with bandages : even if one thigh only is affected, both should be treated. At the end of this period, only disinfected or non-infected clothing should be worn, and, as an additional precaution, unguentum acid. benz. should be applied nightly to the treated areas.

Tincture of merthiolate (Eli Lilly & Co.) is also effective (p. 655).

For the ringworms of the thick-skinned natives, linimentum iodi of double strength, freely applied, is the best, speediest and most efficient remedy, but it is too irritating and painful for the European skin.

Prophylaxis.—The various forms of crutch dhobie's itch may be avoided by wearing next the skin short cotton bathing-drawers and changing them daily, at the same time powdering, after the daily bath, the axillæ and crutch with equal parts of boric acid, oxide of zinc, and starch.

Ringworm of the Feet (Hongkong Foot ; Athlete's Foot ; Brocq's Eczema ; Tinea Pedis)

A peculiarly intractable infection of the soles of the feet, occurring especially amongst Europeans, is commonly observed in China and is known locally as "Hongkong foot." This mycotic infection, as identified by Dodd, is believed to be a variety of *Epidermophyton inguinale*, or, according to Beintemar, *E. interdigitale*. It occurs especially during the summer months and appears as deep-seated vesicles about the inner margin of the hollow of the sole, or on, or between, the toes at their proximal extremities ; or as a macerated condition of the skin of the interdigital clefts and of the contiguous surface ; scaling of the skin with persistent and intolerable itching is a marked feature, and it often becomes secondarily infected (Fig. 118). Often a mycotic infection of the nails and the palms of the hands is associated with it. resembling Hebra's *eczema marginatum*, which is said to be due to a special fungus, *E. floccosum*. A similar condition has been described in Turkish baths in England by Whitfield, and in swimming baths in the Southern United States, as well as among bathers in Holland. As a preventive measure the application of the following lotion is recommended :

Liq. formaldehyd. (40 per cent.)	ʒi	(3·5 c.c.)
Acid. salicyl.	ʒi	(3·5 c.c.)
Alcohol and water, equal parts .	℥viii	(227·36 c.c.)

Care must be taken to distinguish the eczema reactions which are superimposed upon foot ringworm. Where such reaction is present treatment must be directed on other lines.

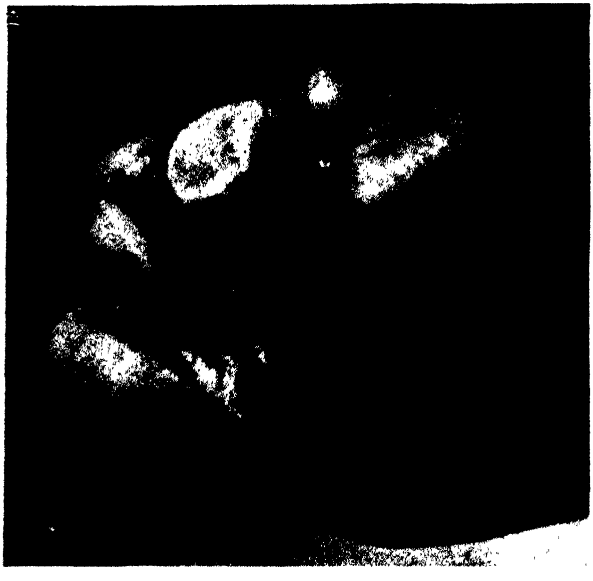


Fig. 118.—Ringworm of the foot.

Treatment.—The application of Whitfield's ointment, after the feet have been soaked in hot water, is recommended : salicylic acid 1, benzoic acid 1, coco-nut oil 12, soft paraffin 16 parts. This ointment must be persisted with for three weeks or more.

Rademacher (1943) recommended the following treatment, which has been found most effective during the present war : 25 per cent. sulphathiazole in talc is dusted on to the lesions daily. Definite improvement appears within forty-eight hours. A commercial preparation consists of 5 per cent. sulphathiazole in a bland ointment and has been found satisfactory. All infected areas should be covered with a film of the powder. The criterion of cure is the healing of all lesions and disappearance of adherent cutaneous débris. In refractory cases 10 per cent. of powdered sulphathiazole is made up with 2 per cent. salicylic acid ointment. The course of treatment lasts from two weeks to one month.

Other authorities favour azochloramide in triacetin, 1 in 500. This penetrates some distance into the tissues and thus enables the germicide —azochloramide—to extirpate the deeper filaments. This preparation N-N—dichloroazo-dicarbonamidine, is a complex chlorine compound, which liberates chlorine slowly.

A preparation which can also be recommended is *Merthiolate cream* (Eli Lilly & Co.) and also tincture of merthiolate, a solution of merthiolate in spirit, which sinks deep into the affected skin and thereby kills off the spores of the fungus.

For eczematous complications the toes should be separated by strips of gauze, and the foot should be covered with it and kept constantly wet with glycerine of lead subacetate, 1 oz., glycerine, 1 oz. and water to 1 pint. This lotion can be later replaced by Lassar's paste. If a staphylococcal infection is present, dressings of acriflavine, 1 in 20,000, should be applied.

As an after treatment Macleod recommended bathing or paddling in sea-water.

Infected patients should take careful precautions against the spread of the fungus, and should wear special slippers in the bathroom. Loofah soles and bath towels are recommended as they can be sterilized by washing.

As a measure against re-infection the patient may wear cotton toe-caps, which must be boiled, and he should also have a rubber bath-mat for exclusive personal use.

RINGWORM OF THE NAILS (*Tinea Unguium*)

This is a mycotic infection of the nails and is a comparatively common and extremely intractable condition in Europeans, especially in India and China ; it may last for twenty years or more. It may occur as an independent affection, or secondary to ringworm of the skin, scalp or beard, and is often found in association with tinea cruris. One or all of the nails of both hands and feet may be attacked. The fungus is a trichophyton, usually *Epidermophyton inguinale*.

The fungus first attacks the epidermis of the nail-bed and gradually invades the nail matrix. In doing so it causes considerable discoloration, ridging and fissuring of the nail itself, which becomes opaque, with a brittle, frayed edge. The fungus may pass from the skin over the nail-fold and in this manner reach the matrix.

Diagnosis.—The appearance of the affected nail is not sufficiently characteristic to be distinguished without microscopic examination. The disease is generally well advanced before it can be recognized. For microscopic diagnosis, scrapings of the nail are boiled in liquor potassæ, or left to soak for twenty-four hours. The scrapings themselves should be made as thin as possible with a piece of glass. The fungus can then be recognized in the softened nail débris, especially in small dark hæmorrhagic spots. The diseases liable to confusion with ringworm of the nails are *eczema*, *syphilis* and, especially, *psoriasis*.

Treatment.—In the early stages, when the lunule is attacked, t disease may be stamped out by softening the affected portion with soluti potash, and painting with tincture of iodine or with a 2 per cent. soluti of corrosive sublimate in alcohol, twice daily. When the nail is complet involved, cure is almost impossible save by extirpation or by avulsic The result is, however, disappointing, as the new nail usually becom infected in turn. After removal, the thickened nail-bed should be scrap and the matrix dressed with a parasitical ointment:

Acid. salicyl.	gr.xxx	(1·944 grm.)
Hydrarg. ammon. . . .	gr.xv	(0·097 grm.)
Vaseline	℥i	(31·1 grm.)

The shedding of the nails by application of X-rays is unsatisfacto Less severe cases are treated by softening the nail-plate by wearing rubb finger-stalls containing soft soap for a few days; the softened nail is th scraped down as far as possible with glass, followed each time by t application of lint soaked in Sabouraud's iodine (iodine 5, potassium iodi 1, water 100), which should be kept in position by a loose rubber finger-sta

Tinea Imbricata

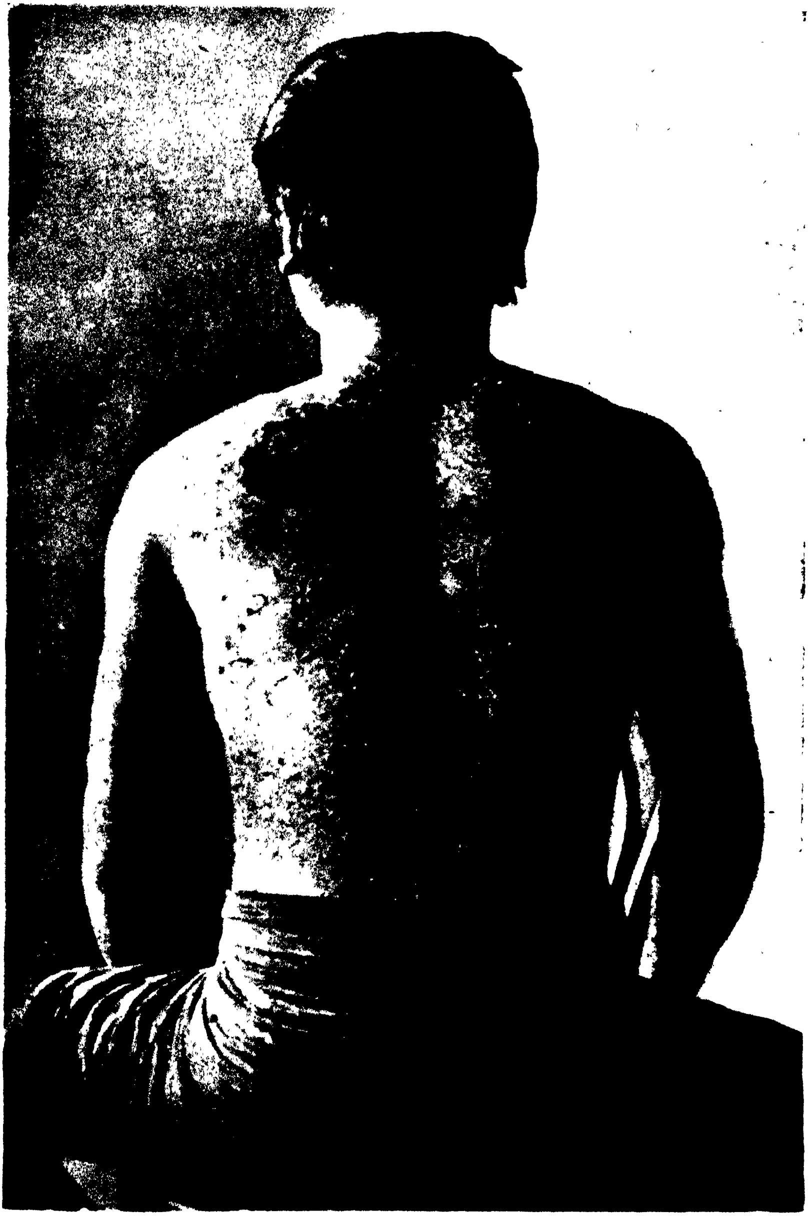
Synonym. Tokelau Ringworm.

Geographical distribution.—The affection is principally met in t Eastern Archipelago and in the islands of the South Pacific, where affects a large proportion of the population. It has been found to exte westwards as far as Burma, and northwards as far as Formosa and Fooch on the coast of China. Cases have been reported from Central Africa an the interior of Brazil. Once introduced, it spreads very rapidly in countri with a damp, equable climate and a temperature of 80–90° F. Very hi or very low temperatures and a dry atmosphere are inimical to its extensio

Ætiology.—On detaching a scale and placing it under the microscop after moistening with liquor potassæ, a trichophyton-like fungus can seen in enormous profusion. The parasite evidently lies between epiderm and rete, and by its abundance causes the former to peel up. As t fungus does not die out in the skin travelled over, it burrows under t young epithelium almost as soon as the latter is reproduced. Hence t peculiar concentric scaling and the persistence of the disease througho the area involved. When the scales are washed off by the vigorous u of soft soap and hot water, the surface of the skin is seen to be cover with brownish parallel lines—evidently the slightly pigmented fung proliferating and advancing under the young epidermis.

The parasite, said to be of two varieties, *Endodermophyton concentricum* a *E. indicum*, can be cultured by immersing the scales in alcohol for five to t minutes and then placing them, one scale to each tube, in glucose broth. Aft five or ten days the scales, if uncontaminated, are transferred to solid medi and growth takes place in three or four weeks.

Symptoms.—Tinea imbricata may at first be confined to one or tv spots on the surface of the body; usually, in a short time it comes occupy a very large area. It does not generally affect the soles and palm although it may do so; nor is the scalp a favourite site. Baker remark



TINEA IMBRICATA.

permission of Medical Department of Sarawak Government.)

PLATE XVIII

SALAR JUNG

PINTA.

(Photo: Dineen, San Francisco.)

PLATE XIX

that it avoids the crutch and the axillæ. With these exceptions it may, and commonly does, sweep over and keep its hold on almost the entire surface of the body, so that after a year or two a large part of the body is covered with the dry, tissue-paper-like scales, arranged in more or less confused systems of concentric parallel lines. This arrangement of the scales is absolutely characteristic of the disease (Plate XVIII).

An inoculation experiment readily explains the production of the scales, their concentric parallel arrangement, and the mode of extension of the patches. About ten days after the successful inoculation of a healthy skin with tinea imbricata, the epidermis at the seat of inoculation is seen to be very slightly raised and to have a brownish tinge. Presently the centre of this brownish patch—perhaps a quarter of an inch in diameter—gives way, and a ring of scaling epidermis, attached at the periphery, but free, ragged, and slightly elevated towards the centre of the spot, is formed. In a few days this ring of epidermis has extended so as to include a larger area.

The scales, if not broken by rubbing, may attain considerable length and breadth; but, of course, their dimensions are in some degree determined by the amount of friction to which they are subjected. Usually, they are largest between the shoulders—that is, where the patient has a difficulty in scratching himself. The lines of scales are from $\frac{1}{8}$ to $\frac{1}{2}$ in. apart.

Diagnosis.—From *ordinary ringworm*, tinea imbricata is easily distinguished by the absence of marked inflammation or congestion of the rings, by the abundance of the fungus, by the large size of the scales, by the concentric arrangement of the many rings or systems of rings, by the non-implication of the hair, and by the avoidance of crutch and axillæ. From *ichthyosis* it is distinguished by the concentric arrangement of the scaling, by the peripheral attachment of the scales, and by the presence of an abundance of fungus elements.

Treatment.—The best treatment for tinea imbricata in natives is the free application of linimentum iodi; its action is said to be increased by the addition of salicylic acid, 15 gr. to the ounce. Limited patches may be treated with chrysophanic acid ointment (20 gr. to the ounce), or by the more modern preparation, cignolin. Clothes should be boiled or burned.

Prophylaxis.—Daniels related that tinea imbricata is a comparatively rare disease in Tonga, and the natives attribute this to their custom of oiling the body with coco-nut oil. Since the Fijians adopted this practice the disease has become somewhat less prevalent among them. Personal cleanliness, and the immediate and active treatment of any scaling spot, should be carefully practised in the endemic countries. Amongst certain Central African tribes, it has never been observed in women, who oil their bodies, whereas the men, who do not adopt this custom, are subject to the disease.

In Tahiti the use of chrysophanic acid is now general among the natives; as a consequence, the disease is less prevalent there than it was only a few years ago.

VII. SPIROCHÆTAL SKIN DISEASE AND AFFECTIONS OF THE HAIRS

Pinta

Synonyms. Caraate ; Mal del Pinto.

Definition.—A spirochætal disease characterized by peculiar pigmented patches on the skin.

Geographical distribution.—Pinta occurs in certain districts in tropical America, especially along the river banks—in Mexico, Venezuela, Colombia, Bolivia, and in one or two places in Peru, Chile, Guatemala, Honduras, and Brazil.

Ætiology.—For many years this peculiar skin disease was regarded as due to parasitic fungi. Herrejon (1927) suggested that the pinta was produced by a spirochæte allied to that of syphilis and yaws. Armenteros and Triana in Cuba (1938) found this organism in the skin abrasions, and Blanco (1938) obtained it by lymph gland puncture. To this spirochæte the name of *S. herrejoni* was given. This discovery was confirmed by Blanco (1938) in Mexico, by Iriate in Venezuela (1939) and by Leon in Ecuador, who found the organisms especially abundant in the early papules. Brumpt (1939) proposed the name *Spirochæta (Treponema) carateum*, but the correct terminology should be *S. herrejoni*, which has priority.

This spirochæte, in measurement as well as in appearance (by darkground illumination), is closely allied to *S. pallida*. When first isolated it is very active, but its motility decreases in about twenty minutes. It is 12 to 18 μ in length, and easily stained by silver impregnation and by Giemsa stain. It is readily dissolved by saponin and dies in a short time in bile. (Fig. 119).

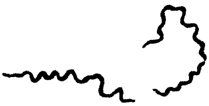


Fig. 119. Spirochæta herrejoni (carateum). (*After Leon y Blanco.*)

Varela claimed that *S. herrejoni* has certain differences from most other spirochætes. When stained by Giemsa it has a flexible cylindrical form with pointed ends. The turns are 0·6–1 μ in width, 0·4–0·5 μ deep and 9–10 in number.

Animal inoculations.—The Venezuela Commission reported that inoculations in guineapigs, rabbits and rats were without result, but Sænz (1940) inoculated the cornea and testes of rabbits with pinta tissues and stated that keratitis and epididymitis, resembling those of syphilis, were produced.

Human Inoculations.—Blanco (1940) demonstrated, by inoculation into volunteers that the disease is infectious and may be easily transmitted when a small amount of serum from a pinta lesion is injected. In syphilitic patients an initial papule developed, but the secondary eruption was atypical. Positive Wassermann reactions were obtained, but not before the appearance of the secondary eruption. The primary lesion differs from that of syphilis or yaws in that it is always closed and does not ulcerate. Experimental inoculations showed that previous syphilis does not give absolute immunity to pinta.

Pathology.—The spirochætes are chiefly located in the Malpighian cells, especially in small areas of acanthosis in the epidermis. A greater involvement of the corium has been described in pinta than in yaws, but much less than in syphilis. Spirochætes may be demonstrated in lymph obtained from glands near the lesions. The hair follicles and portions of the sweat glands are surrounded by inflammatory cells. The pigmentary function is specially affected in pinta, and scanty pigment granules may be seen inside the cells of the stratum germinativum ; they are also present in other cells of the Malpighian layer and in the melanophores of the dermis.

Symptoms.—The incubation period in experimental inoculations varies from 7–20 days, by which time an initial papule appears. This extends peripherally as a squamous, reddish patch, reaching a diameter of 1 cm. in a month, and then continues to spread peripherally. Secondary lesions appear in crops around the primary papule, spreading to other parts in about five months. Progressive hyperpigmentation is then observed ; later still, depigmentation, which gives rise to various colours, or vitiliginous spots, ranging over the body. The colour of the lesions in order of frequency appears to be blue, white, mixed, lead-coloured, violet, black, red or yellow. The spots vary in size and in shape : round, oval or irregular. They are not elevated, but are always strikingly visible (Plate XIX)

In natural infections the primary lesion is usually on an exposed part, particularly the legs and feet and arms, extending to the hands and face. According to Blanco, the initial lesion is never seen on the palms, or on the trunk. Modern observers divide the disease into three distinct stages, showing different clinical, serological and immunological features.

The primary stage occupies the period when the initial lesion is present and lasts from five months to one year. The secondary stage is characterized by skin lesions or papules which are rapidly converted into erythematous squamous lesions (named *pintids*) and ensues five months to one year from the time of infection. In the tertiary, or *dyschromic*, stage there are achromic or pigmentary spots, erythema, keratoderma and superficial atrophy. Super-infections may be produced by inoculations at this stage. Hyperkeratosis of palms and soles, as in yaws, are to be regarded as late manifestations. Eosinophilia and an increase of basophil cells occur in a high percentage of cases.

The exact relationship of pinta to syphilis is further complicated by the fact that Sænz in Cuba found aortitis, aneurysm and enlargement of the diameter of the heart and valvular lesions in 23·3 per cent. The association of this skin spirochætosis with visceral syphilis is of course conceivable.

Diagnosis.—The characteristic spirochætes are present in the lesions, but obviously it is impossible to differentiate them in their morphology from *S. pallida* or *S. pertenuis*. Pinta is often associated with syphilis and yaws lesions, such as juxta-articular nodules. Sænz found changes in the cerebro-spinal fluid in 10 per cent. (increased globulin content and colloidal gold curve).

Depigmented, or vitiliginous areas are common in tertiary yaws and syphilitic lesions in the coloured races to which pinta is almost entirely limited. It is obvious that many other skin diseases have in the past been confused with pinta. Apparently too many examinations have been made for the presence of fungi and micro-organisms without proper cleansing and disinfection of the skin.

Differential diagnosis has to be made from leprosy, yaws, syphilis, erythrasma, pityriasis versicolor and other epiphytic skin diseases, and also from plain vitiligo or leucoderma.

Treatment.—The modern treatment for pinta is neosalvarsan and bismuth preparations, as described for yaws. The superficial skin lesions yield rapidly to salvarsan, but the atrophic vitiliginous spots remain unaffected, as in yaws. The Wassermann reaction in a proportion of cases remains positive after disappearance of the lesions.

TRICHOSPOROSIS

Synonym. Piedra.

This peculiar disease of the hair is very common in certain districts of Brazil, Colombia and British Guiana. It was thought to be confined to the inhabitants of these countries, where a considerable proportion (both male and female, and apparently of all races) are affected, but it has also been found in West Borneo by Kuypers. It has been observed on the eyelashes, beard, and scalp. It is commoner in native women than in men.

The hairs are dotted over at irregular intervals with numerous (1 to 10 or more in a hair 60 cm. in length) minute, gritty nodosities, which feel like sand grains—hence "piedra," sandy. These, barely visible to the naked eye, are distinctly perceptible to the touch when the hair is drawn between finger and thumb. The affected hairs are bent and twisted, and tend to produce matting and knotting. The little nodosities are very firm, but not so hard as the name piedra (a stone) would indicate, being easily cut through with a sharp knife or scissors. They are paler than the hair which they surround, or partly surround, like a sheath. They are situated in the extrafollicular portion and vary from one to ten or more. When a comb is drawn through the hair, a sort of crepitation is produced, doubtless by friction against the hard particles.

In Brazil piedra is known as far as Bahia ; Horta published a monograph there which remains a model of precise observation.

Ætiology.—Under the microscope the excrescences are found to consist of a number of spore-like bodies, *Trichosporon giganteum*, easily made apparent by soaking the hair in liquor potassæ after washing in ether. Langeron has suggested that the correct name for this parasite should be *Piedra hortai* as he considers that it is probably an epiphyte analogous to certain fungi which grow on the leaves in the forests of Central America. The spores are twins, the size of trichophyton spores, and remarkably refringent, and are polyhedral from mutual pressure. Together they form a sort of tessellated mosaic, the elements of which seem to be held together by a greenish soluble cement in which a number of minute bacteria-like rods are incorporated. The shaft of the hair—not eroded or affected in any way—can be seen intact through the encrusting fungus. *T. giganteum* is easily cultivated on ordinary media. It liquefies gelatin in ten or twelve days. The smallest spores measure 2–5μ, the largest up to 12μ. Piedra is supposed by some to be induced by the mucilaginous hair applications in vogue among the Colombians.

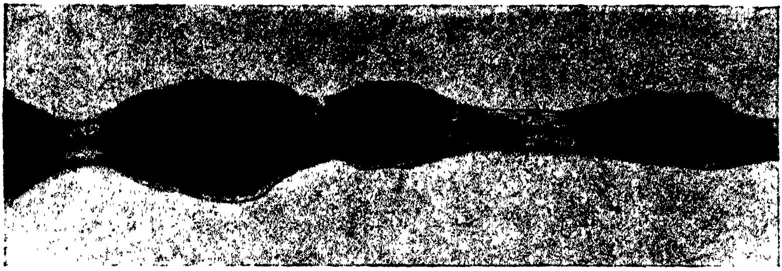


Fig. 120.—Human hair (magnified) affected with *Trichosporon beigeli.*

Diagnosis.—Although Juhel-Rénoy has given to piedra the name "trichomycose nodulaire," the conditions must not be confounded with trichomycosis nodosa, which is a different affection and common enough on the axillary, scrotal and face hair in Europe and elsewhere. Neither must it be confounded with trichorexis nodosa, a non-parasitic disease of the hair-shaft, which is split up at different points into brush-like bundles of fibres, and is thus easily fractured ; nor with moniliform hair, a congenital, hereditary, and non-parasitic condition.

Treatment.– Cleanliness, the free use of soap, and the application of some epiphyticide should suffice for cure ; but should such means fail, doubtless shaving the scalp would be effectual.

TRICHOMYCOSIS

Synonyms. Trichonocardiasis ; Trichomycosis nodosa.

Trichomycosis is a fungous disease of the hair, found in Central Africa and Asia, which in many ways resembles piedra. It may produce skin irritation and stain the clothes. The shafts of the hairs, more especially those in the axilla, are attacked. The parasite is *Trichosporon beigeli* (Rabenhorst, 1867). This has been thoroughly studied by P. Vuillemin (1902). On the hairs it produces irregular nodosities containing the fungus elements, each 3μ to 5μ in length. In cultures, mycelial formation takes place, composed of arthrospores, giving rise to blastospores, and in older cultures to ascospores. The fungus is easily cultivated on Sabouraud's medium, or beer-wort.

This fungus, which was first discovered in London by Beigel in 1862, has been found occasionally in Europe, and is quite common in Japan. It may attack the beard and moustache, which may become matted together so that they cannot be combed out. The affected part emits a peculiar odour, as in the Editor's case from which the illustrations are taken. (Figs. 120, 121.) The hairs have a beaded or nodular appearance and the deposit may vary considerably in colour. The disease may spread to the skin and cause severe intertrigo.

Microscopically, the lesions consist of a mass of polygonal cells, yellowish-green to brown, with a definite cell-wall. The cells of a mycelial thread are separated from one another by thick black cell-walls, between which there is little intercellular substance.

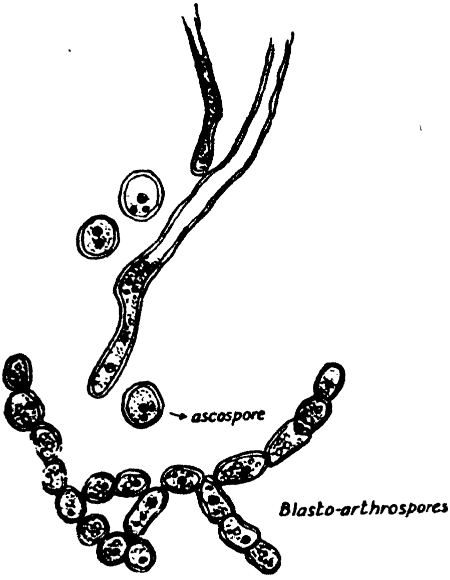


Fig. 121.—Fungus elements of *T. beigeli*.

Treatment. — The affected hair should be bathed twice daily with a lotion consisting of 1 dr. of formalin to 6 oz. of rectified spirit, reinforced by 2 per cent. sulphur ointment. The affected surrounding skin should be rubbed with mercurial ointment.

VIII. SKIN DISEASES CAUSED BY ANIMALS

THE CHIGGER, OR SANDFLEA

This insect, formerly confined to the tropical parts of America (30° N. to 30° S.) and to the West Indies, appeared on the West Coast of Africa for the first time about the year 1872. Since that date it has spread all over the tropical parts of that continent, and even to some of the adjacent islands—Madagascar, for example. As a cause of suffering, invaliding, and indirectly of death from secondary infections, it is an insect of some importance. It is now extremely prevalent on the East Coast of Africa, and is causing a large amount of invaliding among the Indian coolies there by whom it has been introduced into India as far east as Karachi, but in no other part.

The chigger (*Tunga penetrans*) is not unlike the common flea either in appearance or, with one exception, in habit. It is somewhat smaller (1 mm.), the head being proportionately larger and the abdomen deeper than in the flea. It is red or reddish brown. Like the flea, its favourite haunt is dry, sandy soil, the dust and ashes in badly kept native huts, the stables of cattle, poultry pens, and the like. It greedily attacks all warm-blooded animals, including birds and man. Until impregnated, the female, like the male, is free, feeding intermittently as opportunity offers. As soon as she becomes impregnated she burrows diagonally into the skin of the first warm-blooded animal she encounters where, being well nourished by the blood, she proceeds to ovulation. By the end of this process her abdomen, in consequence of the growth of the eggs it contains, has attained the size of a small pea. (Figs. 122, 123.) As seen in Fig. 123, the chigger within the epidermis enters the stratum lucidum;

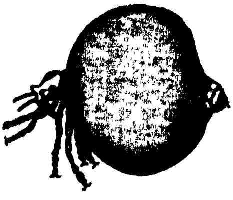


Fig. 122.—Chigger, impregnated female. × 10. (*Blanchard.*)

which it invades and pushes before it. The epithelial layer becomes attenuated. The parasite becomes anchored in the corium by means of chitinous excresences which stick out into the surrounding tissues. The first anterior and the two posterior segments do not participate in the enlargement, the latter acting as a plug to the little hole made by the flea on entering the skin. When the eggs are mature they are expelled by strands of muscular fibres which intersect the abdomen. They fall on the ground and, according to Hicks, the larva hatches on the third or fourth day; the first moult occurs on the fifth to eighth day and preparation for pupation on the sixth to seventeenth days. The larva pupates at the same time, and the imago usually emerges about the seventeenth day. (*See also* Appendix p. 996).

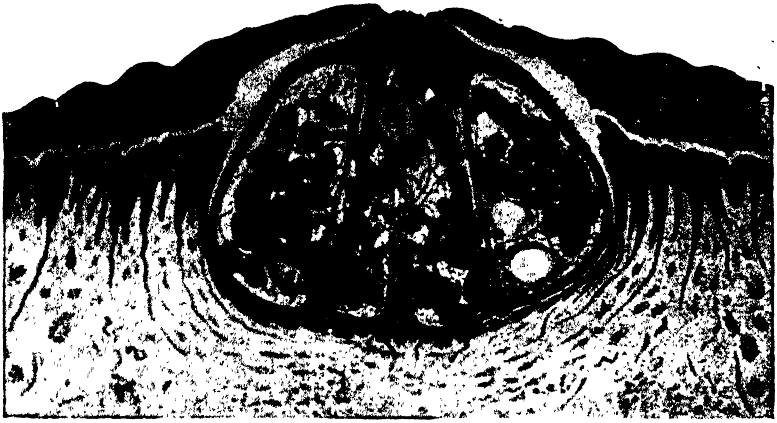


Fig. 123.—Section of female chigger in the stratum lucidum of the skin. (*Fülleborn, Arch. für Schiffs-und Tropenhyg.*)

During her gestation the chigger causes a considerable amount of irritation. In consequence of this, pus may form around her distended abdomen, which now raises the inflamed integument into a pea-like elevation. After the eggs are laid (according to some, before this process) the superjacent skin ulcerates, and the chigger is expelled, leaving a small sore which may be infected by some pathogenic micro-organism, such as the bacterium of phagedæna or of tetanus, with grave consequences (Fig. 124.)

The chigger is not a good jumper and therefore she seldom attacks the skin *above* the dorsum of the foot.

The soles (Fig. 125), the skin between the toes, and that at the roots of the nails are favourite situations. Other parts of the body are by no means exempt; the scrotum, the penis, the skin around the anus, the thighs, and even the hands and face, are often attacked. Usually only one or two chiggers are found at a time; occasionally they are present in hundreds, the little pits left after their extraction, or expulsion, being sometimes so closely set that parts of the surface may look like a honeycomb.

Ulceration is common, and may follow removal of the chigger or natural extrusion of the egg-sac. The ulcer commences as a tiny pit and, as it extends, the sloping edge may develop into septic ulcer. It remains more or less circular in outline, except under the nail or nail margin, where the outline is more irregular and a pocket of pus forms underneath it. Chronic absorption of pus may lead to thrombophlebitis.

Treatment.—In chigger regions the houses, particularly the ground floors, must be frequently swept and accumulations of dust and débris prevented. The housing of cattle, pigs, and poultry demands the same precautions. The floors should often be sprinkled with carbolic water, pyrethrum powder, or similar insecticide, and walking bare-footed must be avoided. A daily bath must be taken, and any chiggers that may have fastened themselves on the skin at once removed. They may be killed by pricking them with a needle, or by the application of chloroform, turpentine, mercurial ointment, or similar means, after which they are expelled by ulceration. The best treatment, however, is not to wait for ulceration, but to enlarge the orifice of entrance with a sharp, clean needle and neatly to enucleate the insect entire. Some native women, from long practice, are experts at this little operation. The part must be dressed antiseptically and protected until healed. Europeans living in an endemic district should wear high boots. A daily inspection of the feet, especially under the nails, is advisable. Should any black dot be discovered, the chigger should at once be removed.

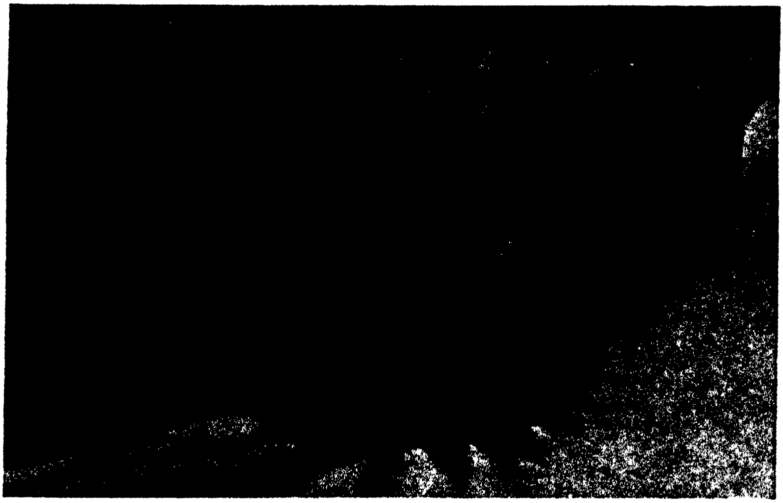


Fig. 124.—Septic lesions of foot caused by chiggers.

Prophylaxis.—If avoidable, camps should not be formed in chigger-infested spots or in the neighbourhood of native villages. The camping-ground should be swept or, if necessary, fired ; the floors of huts and tents may be sprayed with insecticides and naphthaline, and native tobacco dusted inside boots or shoes. Balfour recommended that the feet be rubbed thoroughly with a mixture consisting of 5 drops of lysol, or liq. cresoli sap., in 1 oz. of vaseline. Special attention should be paid to the interdigital clefts. Pigs should not be kept in the vicinity of dwelling-houses, as these animals are severely attacked by chiggers.

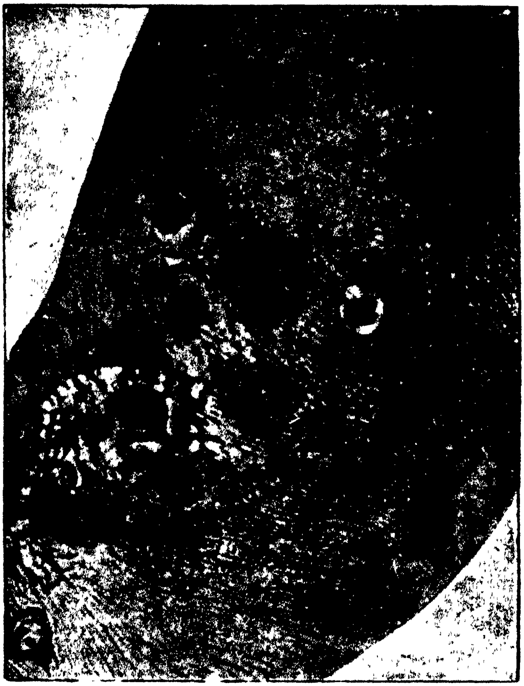


Fig. 125.—Chiggers in sole of foot. (*Dr. C. W. Daniels.*)

ACARINE DERMATOSIS

Several forms of mites inhabiting sugar, grain, or copra may live as

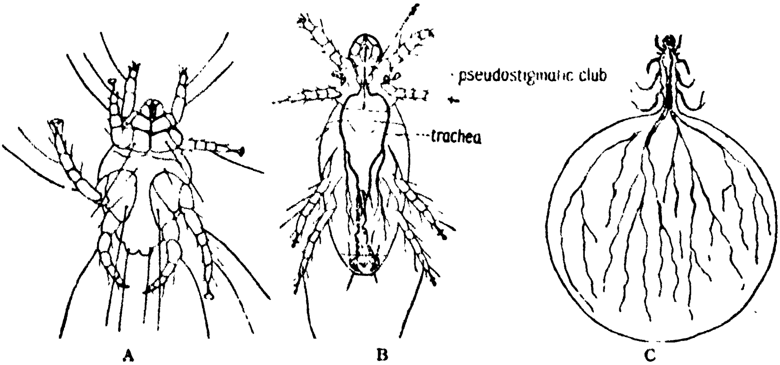


Fig. 126.—*Pediculoides ventricosus.* × 80. (*After Alcock.*)

A, Male ; B, adult female ; C, pregnant female with brood-sac.

temporary parasites on the skin of man, and set up an intense irritation not unlike that produced by scabies. One of the most familiar of these is "grocer's itch," set up by mites of the genus *Glycophagus*, which are common in raw sugar and cause an erythematous rash. Among the copra workers in Ceylon and the Pacific islands a similar skin affection is due to *Tyroglyphus*. "Grain itch," an urticarial and papular eruption of the exposed parts of the body, is caused by *Pediculoides ventricosus* (Fig. 126, A, B, C) in those who handle grain, cotton-seeds, or beans. These mites give rise to a severe pruritus. Preventive treatment consists in the application of 5 per cent. beta-naphthol ointment, and dilute carbolic acid to kill the mites.

Section VIII.—LOCAL DISEASES

CHAPTER XL

TROPICAL PYOMYOSITIS—RHINOSPORIDIOSIS—RHINOSCLEROMA—AINHUM—BIG HEEL—ONYALAI—CHIUFA—TROPICAL ENSINOPHILIA

I. Tropical Pyomyositis

Synonyms. Myositis Purulenta Tropica; Tropical Myositis; "Bungpagga" (Patton).

History and geographical distribution.—In 1912 H. H. Scott described this disease in Jamaica. Deep intramuscular abscesses were associated with pyrexia, and a striking feature was the hard swellings set up by enormous collections of serous fluid. A small bacillus was isolated, which was named *B. serofaciens.*

In the same year Külz found intramuscular abscesses very common in the Cameroons; and in Duala, in 1907–1908, out of 386 natives, 18 were operated on for intramuscular abscesses, and out of 86 Europeans, 5 were thus treated. In natives abscesses were multiple; in Europeans usually single, and they varied in size up to that of a hen's egg. He believed that they were secondary to *Loa loa* infection.

In 1913, Wise and Minnett in British Guiana described what was obviously the same condition, and they failed to find remains of adult filariæ (*Wuchereria bancrofti*) in the pus, though filaria embryos were discovered in seven. Recurrence of abscesses in the same patient was a feature of the disease. In most instances streptococci were isolated from the pus.

Ziemann (1913) described an exactly similar form of intramuscular suppuration in New Guinea, and claimed that already, in 1904, he recognized the disease as one *sui generis* as distinct from suppuration with filariasis. In 1917, E. L. Walker reported upon cases from Brazil. Commes in 1918 met it in French West Africa, where it had previously been noted by Bouffard. In 1922, Laigret and Lefrou, in French Equatorial Africa, remarked upon the deep chocolate colour of the pus, almost resembling liver-pus. Tanon and Jamot (1926) found it common in the Cameroons during the 1914–18 war, when it was known as "*lambo lambo.*" Summaries of our knowledge on this subject have been made by Appel (1921) from the German, and Connal (1930) from the British view-point, and Gibler (1922) gave further details of pyomyositis in Northern Australia and Papua, and James in the Solomon Islands. Van Steenis (1931) recognized the same disease in Java. P. A. Buxton (1928) published a very complete account of myositis as he observed it in Samoa, and was convinced on ætiological grounds that myositis is distinct from the deep suppuration sometimes observed in filariasis. It is of considerable importance in Samoa, and was observed in Europeans, Samoans, half-castes, Chinese, and Melanesians. He found that pulmonary complications were not infrequent, abscesses were invariably intramuscular, suppurative and non-suppurative lesions were common, while *Staphylococcus aureus* was the organism responsible. Grace and Grace (1931) investigated an outbreak, which amounted to an epidemic, in the island of St. Kitts. The outbreak affected more than 300 individuals, with a death-rate of 10 per cent. Some cases resembled septicæmia. The Editor has treated cases in Europeans, Chinese, Japanese, Indians, Negroes and Polynesians.

Ætiology.—The infection was regarded by Pawan as secondary streptococcal and staphylococcal infection in filaria-infected subjects. Grace thought that the causal organism was a hæmolytic streptococcus derived from the throat. Von Bormann thought that the organism was a hæmolytic staphylococcus, usually *S. aureus*, less commonly *S. albus*. Erasmus in East Africa found the former most frequently. In the Editor's experience these two organisms are responsible, though occasionally *Streptococcus pyogenes* is found.

The site of entry is uncertain, but dissemination appears to take place by the bloodstream, for the lymphatics and lymph glands may show no sign of inflammation.

Associated infections.—Pyomyositis is more apt to occur in persons who are debilitated as the result of some other longstanding infection. In the Editor's experience this has been either ancylostomiasis, malaria, and, in a proportion, syphilis. In his series of cases the Wassermann reaction was positive in 50 per cent. One of the chief aims of treatment should be the eradication of these concomitant infections, and, wherever necessary, antisyphilitic treatment with salvarsan and bismuth should be instituted.

Symptoms.—Several types may be distinguished.

Acute non-suppurative stage.—An indurated, tender, ill-defined mass can be felt in the affected muscles where the patient complains of pain. There is usually slight pyrexia, with inflammatory reaction over the neighbouring tissues and pitting œdema. On incision the tissues are œdematous, whilst the regional lymph glands are usually enlarged and tender.

Acute suppurative stage.—The clinical features are those of a deep-seated abscess, and, on incision, large collections of pus in the affected muscles are evacuated. The abscess cavity is loculated, requiring a wide incision and the breaking down of septa formed of dense indurated muscle, or fibrous tissue. The numerous sloughs in the cavity are characteristic. These abscesses occur in widely separated sites : in the thigh muscles, pectoralis major, serratus magnus, latissimus dorsi, gastrocnemius, flexor muscles of arm and iliopsoas and internal oblique. Generalised septicæmia may result.

Chronic abscesses have been recorded in the adductor magnus.

Diagnosis.—The diagnosis of pyomyositis should not present any great difficulty, but it has to be differentiated from gummatous suppuration, filarial abscesses, glanders, melioidosis, rheumatic nodules and swelling, osteitis of femur, cold abscesses of sacro-iliac joint, septic mastitis, perinephric abscess and fibrosarcoma.

Treatment.—The course of events is well illustrated by the case of a European from British Guiana who was treated in 1931. The illness lasted over one year and began as external boils, mostly in the feet and arms. Soon he suffered from febrile attacks, associated with rheumatic-like stiffness of the muscles. Small hard nodules were noted on the leg, thigh, pectoral and submaxillary regions. Stiffness of the legs was caused by diffuse indurated swellings in the extensor muscles, which were due to serous infiltration. During the seven months he was under the Editor's care no less than fifteen inflammatory swellings appeared in various parts of the body, associated with stiffness, pain, and pyrexia. The extensor muscles of the thigh were the seat of several large abscesses. The Wassermann reaction was positive. There was a moderate leucocytosis of 15,000–19,000. From time to time inflammatory periosteal nodules appeared which could be demonstrated by X-rays. There was synovitis of both knee-joints. Eventually, a large abscess appeared in the right pectoralis major muscle, leading to partial necrosis of the eighth rib, which had to be resected. The organism responsible was *Staphylococcus aureus*. The patient eventually recovered after eight surgical operations and prolonged antisyphilitic treatment with bismuth and neosalvarsan. Combined treatment with a vaccine of *Staphylococcus pyogenes aureus* was fairly successful. Earle thinks that surgical treatment is best, combined with intensive sulphonamide therapy, especially sulphapyridine and sulphathiazole.

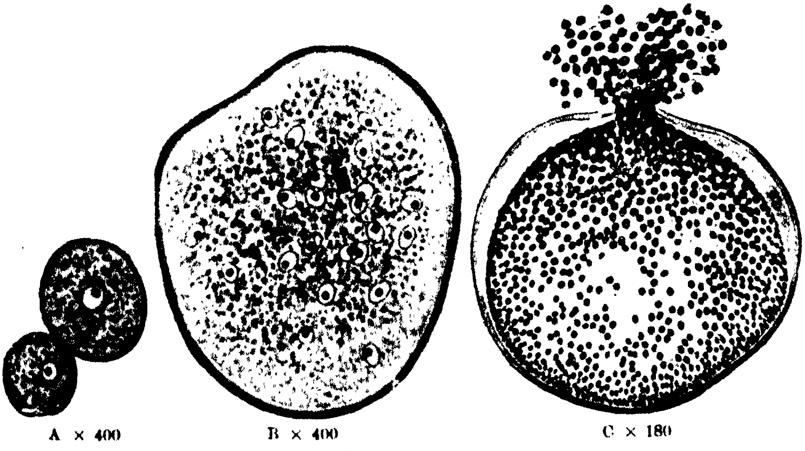
II. Rhinosporidiosis

Definition.—A disease due to a yeast-like organism, *Rhinosporidium seeberi*, which infects the mucous membrane of the nose, producing nasal polypi and tumours on the cheek, conjunctiva, lachrymal sac and uvula.

History.—*R. seeberi* was first described in Argentina (1896), and considered to be a protozoon allied to *Coccidium*. Subsequently it was found in nasal polypi by O'Kinealy in 1903, when the organism was described by Minchin and Fantham. Ashworth (1923) thought that the organism is probably a yeast, or phycomycete.

This parasite has now been recorded from India, Ceylon, Argentina, Uganda (Mowat and Hennesey, 1941), and the United States.

Ætiology.—*Rhinosporidium seeberi* (Wernicke, 1903) is a spherical or oval non-motile organism which occurs in polypoid growths, usually lying between the connective-tissue cells. The earliest stages are about 6 μ in diameter, with a chitinous envelope, vacuolated cytoplasm, and vesicular nucleus containing a karyosome (Fig. 127, A, B). When fully-grown, the cyst, or sporangium, may measure 0·25–3 mm. in diameter, but when half-grown the nucleus commences to divide by binary fission, until thousands are produced, of which the majority become daughter-spores, though a considerable proportion remain unchanged. The fully-formed sporangium (Fig. 127, C) finally bursts and discharges the spores, which are enclosed in chitinous envelopes; they then



A × 400 B × 400 C × 180

Fig. 127—*Rhinosporidium seeberi.* (*After Ashworth; by permission of Roy. Soc. of Edin.*)

A, Trophic stages. B, Section of a stage with 64 nuclei, 24 of which lie in this section. C, Sporangium from which spores are being discharged, accompanied by mucoid substance, through a wide orifice. The first spores to issue (those near the opening) are followed by the central spores. The peripheral spores lie in a fairly firm mucoid matrix. Stretching of the envelope, due to growth of the sporangium, has not only reduced its thickness, but has almost caused the disappearance of the thickened annulus round the pore.

spread into the connective tissues *via* the lymph channels, and on reaching suitable spots the trophic stage at once begins and the cycle is repeated.

Attempts at cultivation proved partially successful in Ashworth's hands, and multiplication of the spores took place, but slowly, on Sabouraud's medium.

The mode of transmission of this parasite is undetermined, but the occurrence of a closely related organism, *R. equi*, in the nasal cavities of the horse is suggestive.

Treatment consists in removing the polypi from the nares by a wire snare. Medical treatment does not appear to be indicated, although Wright reported that the tumours disappear after intravenous injections of tartar emetic. Allen (1936) used neostibosan though it is not always effective. A popular native remedy is a snuff composed of tobacco leaves and lime.

Fig. 128.—Rhinoscleroma of two years' duration in an Egyptian woman.
(Dr. H. K. Giffen.)

III. RHINOSCLEROMA

Rhinoscleroma (*Scleroma respiratorium*) (Fig. 128) is a well-marked disease in all its aspects, pathological or bacteriological. It has a world-wide distribution, but at the present day is much commoner in the Tropics than elsewhere. It takes the form of spontaneous, painless, and exceedingly chronic inflammatory growths occurring at any place in the respiratory passages from the nostrils to the hilum of the lung. Gross deformity of the nose, or narrowing or distortion of the respiratory passages results. Sometimes there is perforation of the nasal septum with total destruction of the uvula. The process extends along the respiratory passages with little change in the surrounding tissues; on the whole, it tends to form metastases with enlargement of the neighbouring lymphatic glands, but, in spite of this, the general health and condition remain unaffected.

Geographical distribution.—Rhinoscleroma is spread over widely distributed regions in special nests, or foci, but occurs all over the world. The most extensive region is in Eastern Europe, in Hungary, Poland, the Ukraine and the northern shores of the Black Sea and Caspian. Other foci have been noted at Tomsk in Siberia, in Turkestan, Bengal, Java, Sumatra, central and southern France, Morocco, Egypt, North America (in New England states), Cuba, Mexico, Panama, Colombia, Brazil, Peru, and Chile.

Ætiology.—The cause of rhinoscleroma is undoubtedly the *Bacterium* (*Klebsiella*) *rhinoscleromatis* described by V. Frisch in 1882. It is closely related to *Bact. pneumoniæ*, and is usually Gram-negative. It is easily cultivated, and forms knob-like colonies on gelatin or agar, greyish on the whole, and less conspicuous than *B. pneumoniæ*. It usually coagulates milk, and forms acid freely with lactose. In sections, it is found in hard fibrotic swellings in the nose, scattered throughout the mucosa and submucosa. It has so far been found impossible to reproduce the lesions by inoculation, either in man or animals. In fact, it exhibits a very low order of pathogenicity for laboratory animals, with the exception of mice.

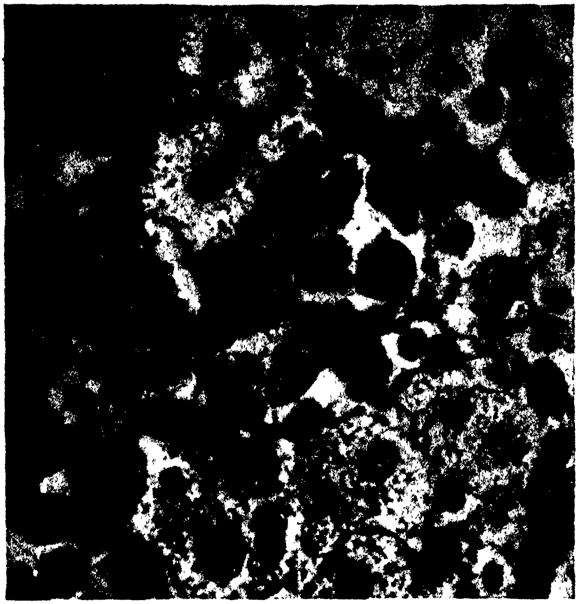


Fig. 129.—Rhinoscleroma : Photomicrograph of tissue, showing Mikulicz cells and general histological picture. (*Dr. H. K. Giffen.*)

It has to be differentiated from other encapsulated pneumococcus-like organisms in the nose.

Pathology.—Rhinoscleroma is characterized by a peculiar form of plasma-cell infiltration of great density, and by gaps or " fat-cells," which are found to consist of swollen cells with foamy cytoplasm (" foam-cells " or " Mikulicz cells ") (Fig. 129). Very frequently, also, there are hyaline-drops or Gram-positive " Russell's bodies," which occur in all kinds of degenerative tissues, and are probably derived from the plasma cells. The rhinoscleroma nodule is known as plasmoma (Unna) ; it never breaks down, but becomes progressively sclerosed.

Treatment. —The treatment is mainly by plastic operation to remove the unsightly outgrowths.

Various other methods, the most important of which is X-ray therapy, have been tried. Intravenous injection of tartar emetic, as in bilharziasis or ulcerating granuloma, has been advocated by some. It is a curious fact that complicating febrile diseases, such as erysipelas, typhoid or typhus fever, may cause healing of rhinoscleromatous growths. This has led to a trial of inoculated malaria or protein-shock therapy, with encouraging results.

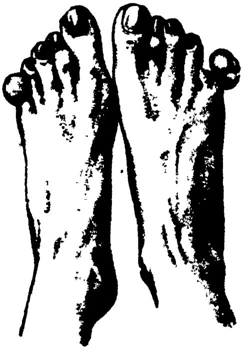


Fig. 130.—Ainhum.

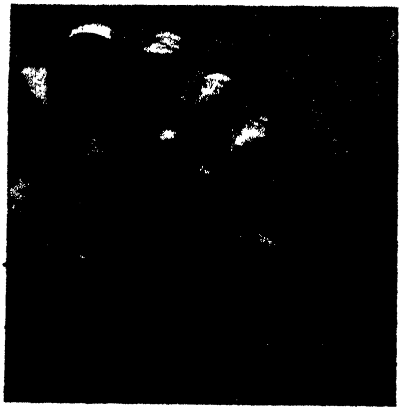


Fig. 131.—Ainhum at its height.
(*Dr. A. B. Filho.*)

IV. AINHUM

This is a very peculiar disease affecting the toes, particularly the little toes, of negroes, East Indians and other dark-skinned races, both in the Old and the New World. The name, derived from the Nago dialect, means " to saw or cut."

Symptoms.—The disease commences as a narrow groove in the skin, almost invariably on the inner and plantar side of the root of the little toe. It may occur in one foot only, or in both feet simultaneously, or it may affect one foot after the other. The groove, once started, deepens and extends gradually round the whole circumference of the toe. As it deepens—perhaps though not necessarily, with ulceration—the distal portion of the toe is apt to swell to a considerable size, as if constricted by a ligature (Figs. 130, 131). There is little or no pain, although there may be inconvenience from the liability to injury to which the dangling and now everted toe is exposed. In the course of years the groove slowly deepens, and finally the toe drops off, or is amputated. The groove may or may not correspond with a joint. In rare instances, after the two distal phalanges have dropped off, or been amputated, the disease recurs in the stump, and the proximal phalanx in its turn is thrown off. Of the other toes, the fourth is the one which is most frequently affected; very rarely is the third, second or great toe attacked. In the Army Medical Museum at Washington, U.S.A., there is a wax model representing a case of this or a similar affection, in which all the toes had been thrown off and the disease was making progress in the leg.

Occasionaly, the terminal phalanx of the fifth digit of the hand has been affected.

Ainhum is very rare in women or children, being most common in adult males. It runs its course in from one to ten or even more years.

On section, it is found as a rule, though not invariably, that the panniculus adiposus of the affected toe is much hypertrophied, that the bone is infiltrated with fatty matter, and that the other tissues are correspondingly degenerated. Sometimes the bone is thinned, or even altogether absorbed. At the seat of constriction a line of hypertrophy of the epithelial layers, and of atrophy of the papillary layer of the skin, together with a band of fibrous tissue, more or less intimately connected with the derma, surrounds, in whole or in part, the narrow pedicle.

Treatment.—It has been suggested that division of the constricting fibrous band would delay the evolution of the disease. In the early stage this might be tried. When troublesome, the affected toe should be amputated. It is said that the application of salicylic ointment delays the process in the earlier stages (Moreira).

V. Big Heel, or Endemic Hypertrophy of the Os Calcis

Maclean described a peculiar form of enlargement of the os calcis which he observed at Kaziankor, Gold Coast, among Fantis and Kroos. The disease begins somewhat suddenly, being preceded by fever, and attended by pain and tenderness which reach their maximum in about a month, gradually diminishing during the succeeding one or two months. Concurrently with the pain there is a swelling of the external surface of the os calcis, rarely of the other tarsal bones.

Maxwell reported a similar condition in natives of Formosa. As in Maclean's cases, the patients were young adults from twenty to twenty-five years of age.

VI. Onyalai (Essential Thrombocytopenia)

Under this title Massey and, later, Wellman (1904) originally described a peculiar disease occurring among the natives of Portuguese West Africa. Since then it has been recognized in East Africa, Tanganyika, on the Congo, and in Northern Rhodesia, where it is known as "Chilopa," "Kafindo," or "Akembe," (bleeding disease—Wallace). It is not usually seen outside Africa, though Preston Maxwell in 1901 described a somewhat similar condition in the Fokien region of South China. It is characterized by formation of a number of vesicles, distended with blood, from ⅛ to ¾ in. in diameter, on the hard palate and on the inside of the cheeks. Some of them are umbilicated. They differ from ordinary blood blisters by the presence of numerous trabeculæ and by the semi-coagulation of the contents which makes the vesicle difficult to empty. Occasionally it is accompanied by fever and, although Massey's original cases, with one exception, recovered within a week or ten days, natives regard the disease with dread, owing to its reputation for deadliness.

The majority of victims are young adults. The onset is sudden and the early symptoms are lassitude, general dullness, and suffusion of the conjunctivæ, with pyrexia, sometimes of 103–104° F. There is tenderness over the parotids and vague pains. These are soon succeeded by widespread hæmorrhages into the skin and mucous membranes. In natives the cutaneous hæmorrhages are most easily seen in the axilla. Stein and Miller remark the constant association of cutaneous *purpura*, which is easily missed on black skins. Bullæ are seen on the lips, buccal mucosa, tongue, and palate, the last-named in particular. Epistaxis occurs in practically every case and subconjunctival hæmorrhages are in evidence. Bleeding occurs from the bowels as well as from the bladder. At autopsy hæmorrhagic vesicles are found in the serous membranes, the pleura, peritoneum and diaphragm. A common finding is hæmorrhagic bronchopneumonia. Usually there are large retroperitoneal perirenal hæmorrhages. Blackie found involvement of the central nervous system in one of his cases. The bleeding time of the blood is increased, and there is a reduction in blood platelets. Normoblasts may be present. The blood sedimentation rate is slightly increased. Blackie thought that onyalai is an acute form of essential thrombocytopenia due to defective nutrition. Stein and Miller (1943), who carried out a fine piece of work, found that onyalai is not confined, as had been thought, to native races. It is quite common in the Transvaal and Northern Bechuanaland. In Africa it extends from the equator to 26° south latitude, Johannesburg being the most southerly point. They studied 21 cases which could be classified as mild, severe or acute. The youngest patient was a native female aged 7 months. Hæmorrhagic bullæ are peculiar to onyalai, and not found in other forms of thrombocytopenic purpura, suggesting some toxic factor. The course of the disease is aggravated by the menses in women, and response to treatment is similar to the acute incipient episodes of idiopathic thrombocytopenic purpura.

The diagnosis has to be made from snake-bite, in which hæmorrhagic symptoms may supervene.

Blackie found that the most effective treatment was by blood transfusions and by injection of 18 c.c. of donor's blood intramuscularly into the buttocks or outer aspects of the thighs, but Stein and Miller found the intravenous route better. They suggest that splenectomy is indicated in patients who relapse after this treatment.

VII. CHIUFA ("CHINKUMBI" AND "KANYEMBA")

This is a disease resembling acute gangrenous rectitis described in the earlier editions of this manual, which has been reported from South America. Gilkes described cases he had under his care in Northern Rhodesia. It is found in the Luangwa and Lusenfwa valleys at an altitude of 2,000–2,500 feet. Its onset is sudden and it runs an acute course. The primary manifestation is stated to be a white powdery condition which appears round the anus and gives the appearance of "boracic acid or flour"; in women it covers the vulva as well. After a few days this disappears and the patient becomes acutely ill with pains in back and neck and a temperature of 104° F. The anus becomes relaxed and the rectum can be seen protruding, red and angry. Throbbing in the rectum is noted, and constipation is the rule. The inflammation travels up the large intestine until the colon is involved, when there may be diarrhœa and vomiting. In women the vagina also may be affected.

VIII. TROPICAL EOSINOPHILIA

A new entity was described by Frimodt-Möller (1940) and Weingarten (1943) in India. This is characterized mainly by spasmodic bronchitis, leucocytosis and high eosinophilia. It affects mostly people who live by the sea, and has apparently no relationship to any other disease but is thought to be a form of allergy. The physical signs are those of bronchial asthma. During the febrile periods the spleen is moderately enlarged. The most striking feature is massive eosinophilia, which accounts for the considerable leucocytosis. It may reach 90 per cent. and is higher than in any other disease, except eosinophilic leukæmia. The X-ray shows disseminated mottlings in the lung, the average single focus being the size of a split pea, somewhat similar to silicosis. The disease is benign and lasts for years, but reacts to intravenous injections of neoarsphenamine in courses of six doses of 1·15 to 0·45 grm.

This description closely resembles that of *Löffler's syndrome*, which is like pulmonary tuberculosis (Freund and Samuelson, 1940). The cause is unknown. Engel in China (1936) and Koino in Japan ascribe it to allergy from privet blossoms, but this has not been observed elsewhere. In some respects it resembles pulmonary coccidioidomycosis (*see* p. 609).

The discovery by Carter and his colleagues (1944) of mites (*Tyroglyphus* and *Carpoglyphus*) in the sputum of these patients is interesting, but awaits confirmation. It is possible that the syndrome may be evoked by sensitization to intestinal parasites, such as *Ascaris* or *Ancylostoma* (*see* p. 765).

Section IX.—ANIMAL PARASITES AND ASSOCIATED DISEASES

CHAPTER XLI

PARASITES OF THE CIRCULATORY SYSTEM: BILHARZIASIS (SCHISTOSOMIASIS)

Definition.—A group of diseases caused by certain digenetic trematodes of the family Bilharziadæ which inhabit the venous system of man in various tropical and subtropical countries.

I. Genito-urinary Bilharziasis (*Bilharzia hæmatobia*) or *Schistosomiasis*

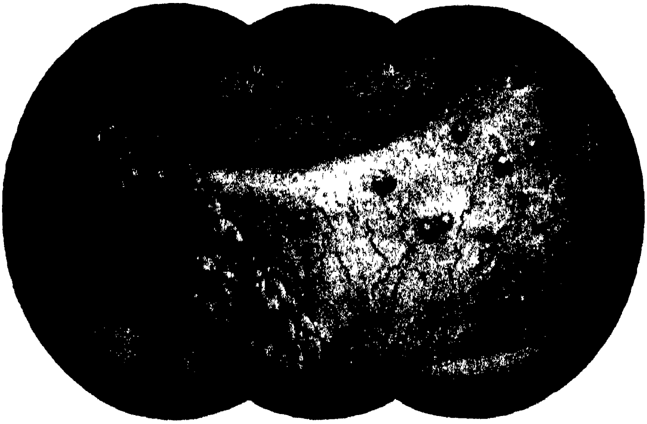
Synonyms. Schistosomiasis; Bilharziasis; Bilharzia Disease; Endemic Hæmaturia.

Definition.—A chronic endemic disease produced by infection of the pelvic veins, particularly those of the bladder, and occasionally those of the rectum, by *Bilharzia hæmatobia*, the eggs of which, being deposited in the mucous membrane, give rise to hæmaturia, cystitis or other symptoms connected with the urinary organs, and occasionally, when deposited in the rectum, to muco-sanguineous discharges from the bowel. The eggs of the parasite are discharged in the urine and, in certain cases, in the fæces.

History.—Hæmaturia has been known to exist in Egypt since the earliest times, and the eggs of this parasite have been found in mummies by Ruffer. Bilharz, in 1851, originally discovered the parasite, which was named *Bilharzia* by Cobbold in honour of its discoverer, but until quite recently it was considered that the generic term *Schistosoma* of Weinland had scientific priority.

Geographical distribution.—The eggs of this parasite were identified by Harley in Natal in 1864, and since then the disease has been found in other parts of Africa, more particularly along the eastern side of the continent, as far south as Port Elizabeth, and it is common throughout the Union of South Africa, especially in Natal. In Central Africa it occurs in the Northern Sudan, Uganda, the Congo, Rhodesia and in North Abyssinia; it is met with in West Africa as well, especially in Liberia and Sierra Leone. In North Africa it is especially common in Morocco, Algeria, Tunis and Egypt. It also occurs in Arabia, parts of Palestine near Jaffa, Persia, Iraq, Cyprus, in the town of Tavira in Portugal, in Mauritius, Réunion, and Madagascar. A few indigenous cases were reported, over forty years ago, from Western Australia. (Map V).

Precise information about the ravages of bilharziasis in Egypt are forthcoming. Scott, as the result of 40,000 examinations, found that in the northern and eastern edge of the Delta, reaching as far as Cairo, 60 per cent. of the inhabitants are infected with *B. hæmatobia*, and an equal number with *B. mansoni*; in the apical southern half of the Delta, however, though still 60 per cent. are infected with *B. hæmatobia*, only one-tenth of that number have *B. mansoni*. The line between the first and second areas is sharp and defined,



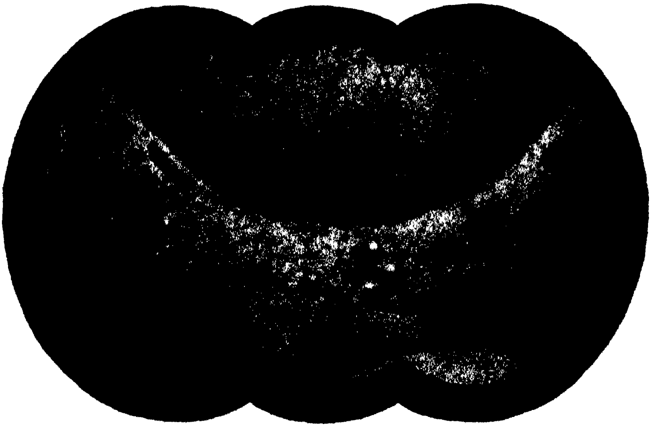


Fig. 2

Bilharzial disease of the bladder before treatment, and one month after treatment with sodium antimony tartrate. The yellow nodules in Fig. 1 are the dead ova working their way through into the bladder cavity. They do not indicate active bilharzial disease.

(By permission of Brit. Journ. Surgery and Dr. J. B. Christopherson.)

BILHARZIASIS OF THE BLADDER.

Plate XX

and does not correspond to any noticeable topographic, hydrographic or demographic variation. Moreover, there appears to be no difference in the number of planorbis snails, the intermediary hosts of *B. mansoni*, in these two regions. In the northern two-thirds of that part of the Nile Valley between Cairo and Assiut, *B. hæmatobia* infects 50 per cent. of the population, but *B. mansoni* and planorbis snail are absent. In the southern third, where old *basin* irrigation—that is irrigation at flood Nile—takes the place of the new perennial irrigation, *B. hæmatobia* alone is present, but infects only 5 per cent. of the population. Heavy infection with *B. hæmatobia* is associated with perennial irrigation from high-level canals, which takes the place of flood irrigation, with alternate flushing and drying. In the district where 5 per cent. of the inhabitants are infected with *B. hæmatobia*, 1 in 1000 die from this infection : in the Northern Delta district, this proportion rises to 1 in 22 (Fig. 248B).

Ætiology. *Parasite.—Bilharzia hæmatobia* is a unisexual trematode. The *male* measures 1-1·5 cm. in length by 1 mm. in breadth ; its cylindrical appearance is due to the infolding of the two sides of the body to form a gynæcophoric canal. The *female*, darker, but longer, 2–2·5 cm. in length, is partially enclosed in the gynæcophoric canal of the male. The parasites live in the blood of the portal vein and its mesenteric branches, but numbers dwell also in the pubic, vesical, and uterine plexuses. The longevity of this parasite is phenomenal, as it may remain active and produce viable eggs for more than thirty years.

The *eggs* are oval, and are provided at one end with a definite spine. They measure 0·16 mm. by 0·06 mm. Normally they are voided in the urine, exceptionally in the fæces. It has been pointed out by Khalil that the hatching of the egg in water is due to osmotic pressure ; a 0·75 per cent. salt solution completely inhibits this process.

Life-history.—On coming into contact with water, the eggs hatch and give rise to an active, ciliated embryo or miracidium, which, as a rule, enters a fresh-water snail, usually of the genus *Bulinus* ; in the liver or hermaphrodite gland of this mollusc it develops into sporocysts, eventually into active, bifid-tailed cercariæ which, on escaping from the snail, re-enter man by burrowing through his skin. Some cercariæ pass through the lung capillaries to the heart and are distributed all over the body, including the skin. Many are held up and die, giving rise to a secondary cutaneous reaction with wheals and blotches due to breaking down of cercariæ. Those which get to the mesenteric capillaries of the bowel wall reach the portal system where they grow until almost sexually mature and become paired. They then return against the stream to the mesenteric veins to lay eggs. (For further details regarding the life-history of this parasite, *see* p. 890.)

Pathology.—The changes brought about by the bilharzia vary very much according to the degree and duration of the infection (Plate XX). In almost every case the walls of the urinary bladder are early affected. All that may be apparent to the naked eye at this stage is a certain amount of injection of the small vessels of the mucosa vesicæ, and certain exceedingly minute vesicular or papular elevations of the surface of this membrane. When these minute elevations are examined microscopically they are found to contain eggs even in minute blood-vessels. Later, especially in the trigone of the bladder, there are rounded patches of inflammatory thickening which project somewhat, are granular on the surface, and dense ; on section they creak under the knife as if they contained gritty particles. It is evident that these elevated, thickened patches are the result of an inflammatory process provoked by the clusters of eggs which the microscope reveals scattered throughout their entire extent. The eggs are principally deposited in the submucosa, less extensively in the mucous membrane, still less abundantly in the muscular walls of the organ or in its subserous connective tissue. They tend to occur in groups, each of which is invested with a connective-tissue capsule ; or they may be lying in small blood-vessels which they occlude. Some eggs are seen to have undergone calcification ; others are still fresh, either segmenting, or already containing a miracidium. On the surface of the rounded patches already mentioned, phosphatic deposits, also containing eggs, are not uncommon ; from their yellow glistening appearance they are known as " sandy patches ", and sometimes they present minute sloughs. (Fig. 133.) Besides these indurated patches, various forms of polypoid excrescence—sometimes ulcerated—may protrude from the mucous surface into the cavity of the bladder. These various hyperplasiæ frequently contain the adult parasite as well as eggs. Ferguson and others described a nodular form of bilharziasis, an affection of the subperitoneal surface of the bladder, which closely resembles tuberculosis.

In addition to what may be designated the specific changes in the mucosa, the muscular coats of the bladder are generally hypertrophied. In consequence of this, as well as of the ingrowth of villosities and different forms of new growth, the capacity of the organ may be much diminished. Its mucous surface is generally coated with a sanguineous mucus containing myriads of eggs. Gravel or small stones—generally phosphatic—are sometimes found either embedded in lacunæ in the hypertrophied and roughened bladder-wall, or free in the cavity. Not infrequently a similar hyperplasia occurs in the ureters, and particularly towards their lower ends, even at an early stage. In rare instances the pelvis of the kidney is affected. Obliteration of the ureter, both from small stones and from thickening of the mucous membrane, not infrequently results ; this leads to dilatation of the pelvis and atrophy of the parenchyma of the kidney. It is easy to understand how, in time, these changes in the bladder and ureters may give rise to hydronephrosis, pyelitis, abscess of the kidney, and similar secondary affections. Hyperplasia of the prostate due to infiltration with eggs is sometimes found.

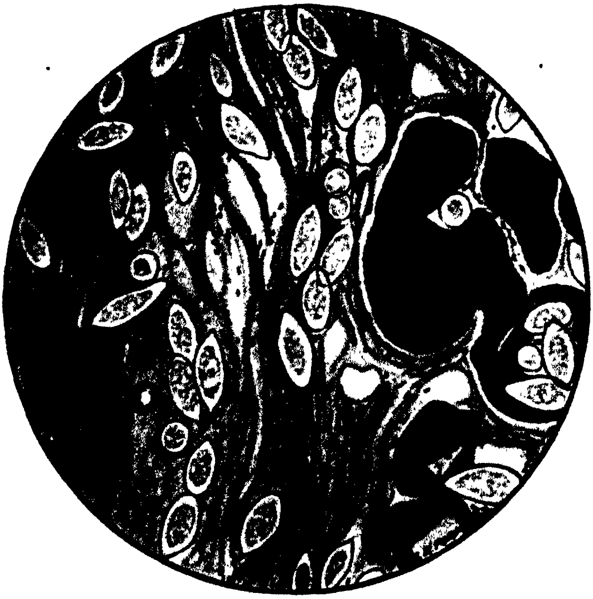


Fig. 132.—Section of bladder-wall, showing eggs of *Bilharzia hæmatobia* in tissues.

Hyperplasia from bilharzial infestation may also occur in the vesiculæ seminales, penis, walls of the vagina, and cervix of the uterus, leading to corresponding bloody, egg-containing discharges.

Bilharzia eggs in small numbers have been found in the liver, in gallstones, in the heart, and in the kidneys, and occasionally in the brain, spinal cord, and lungs. Tumours of bilharzial origin have sometimes been met in connection with the peritoneum and ligaments of the uterus. The egg-production of *B. hæmatobia* is slower than that of *B. mansoni.* They get to the lowest branches of the mesenteric veins, some even to the rectum, when eggs may appear in the fæces, but most migrate through the hæmorrhoidal vein to the venous plexus of the bladder. When the eggs are deposited eosinophil cells are attracted and may produce micro-abscesses, forming pseudotubercles on the peritoneal surface of the bowel with resulting connective tissue. If they occur on mucous surfaces they take the form of small erosions or ulcers. Giant cells form and may completely absorb the egg.

The eggs can be conveniently demonstrated in the tissues by digesting selected portions in 3 per cent. potash solution.

Symptoms.—The symptoms produced by *B. hæmatobia* vary in degree within very wide limits. In the vast majority of cases the patient experiences no trouble whatever; in other instances suffering is very great. Indirectly, from the serious lesions of the urinary organs to which it may give rise, this bilharzia is an occasional cause of death.

Early toxic symptoms, such as pyrexia with urticaria, have been noted, and may come on four weeks after exposure to infection. The *incubation period* of definite disease, on the other hand, varies from three months up to two and a half years. The cercariæ, on penetrating the skin, produce an irritative dermatitis as in other forms of bilharziasis. (*See* p. 693).

The most characteristic symptom of the presence of the parasite in the wall of the bladder is the passage of blood at the end of micturition, with or without a sense of urinary irritation. The quantity of blood passed and the degree of irritation are increased by exercise, by dietetic indiscretions, and by all such causes as are calculated to induce or aggravate cystitis. As a rule, it is only the last few drops of urine that contain blood; sometimes, however, the hæmorrhage is more extensive, and then the entire bulk of the urine may be blood-tinged. Occasionally, clots are passed.

If, in a case of moderate infection, the urine be passed into a glass and held up to the light, minute flocculi or coiled-up mucoid-looking threads will be seen floating about in the fluid. If it be allowed to stand, the flocculi, and perhaps minute blood-clots, will subside to the bottom of the vessel; these, on being taken up with a pipette and placed under the microscope, will be found to contain, besides blood-corpuscles and catarrhal products, large numbers of the characteristic terminal-spined eggs.

In doubtful cases, where eggs are few, the best way to find them is to get the patient to empty the bladder and to catch in a watch-glass the last few drops of urine which can be forced out by straining; these invariably contain eggs. A low power of the microscope suffices, and is best for diagnosis. Davies in South Rhodesia has remarked upon the peculiarities of the "bilharzial facies," which becomes triangular in outline, with sunken cheeks and prominent malar bones. He considers that this appearance forms a good indication of the disease.